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THE NATURAL HISTORY OF INFECTIOUS DISEASE IN A BOYS' SCHOOL, 1900-1956*

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BOSTON

THE charts to be presented sketch in profile the natural history of measles, mumps, chicken pox, rubella, influenza, hepatitis and poliomyelitis in a universe of high-school boys throughout the twentieth century to date. Such information is, as far as I know, unique.

Located in a small town about 25 miles from Boston, the St. Mark's School structure is an extended H-shaped building containing classrooms, dormitories, dining room, library, chapel and infirmary. An average annual enrollment of about 195 boarders, practically all of teen age, represents a gradual increase in population from 130 at the turn of the century. A pleasant surprise for me on taking over as director of health after returning from military service in 1946 was to find that the system of medical recording has remained unchanged since 1898. Somebody, I am glad to say, with an almost obsessional sense of collecting, had saved all the morning reports, which had accumulated for half a century beneath a window seat. This was opened once a year when the new year's additions were stuffed in; and I am glad to report that the stuffing process continues — into file drawers instead of window seats.

I select one of these records of April 16, 1900, to illustrate the kind of information listed every morning in a morning report forwarded to the Headmaster; it gives a patient's name, his temperature and his diagnosis. There is little reason for questioning the clinical accuracy of the diagnoses of most of the infections that will be analyzed. For example, the clinical opinion of the school physician that young Willard had an "eruption like German measles" was confirmed by a typical outbreak of 23 cases of rubella that appeared two and a half weeks later. As will be demonstrated graphically, this sequence of events took place fifty-six years ago in April after the Easter holidays.

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MEASLES

However, it is measles (Fig. 1) that ushers in January, 1900, with an outbreak involving over 10 per cent of the school. Cases are arranged by three-day intervals for the first twenty-seven days of a month, the tenth interval covering a period of either three or four days, as the case may be, in every month but February. Rates are not given, and the outbreaks are charted in actual number of cases. Since the population remains reasonably stable from year to year the eye can see the whole fifty years at a glance. Thus, it is readily apparent that outbreaks of measles occurred 4 times in the first twenty-five years of the century when the closed community was more closed than it became in the automobile age. Most of the boys arrived by train in the fall and left by train at Christmas. Arriving back after New Year, they settled in until Easter vacation, and when they returned it was to stay until June. Epidemics of measles occurred twice as frequently in the second twenty-five-year period — the automobile era suggesting a speed-up in the transfer tempo of infection. If this is so, the expectation would be that measles would migrate right out of the high-school age down toward the nursery-school population; and the facts are consistent: on 4 occasions in the past twenty years the introduction of the disease has not resulted in secondary cases. There have been only 7 cases since 1950; yet the boys are about 90 per cent immune by history.

MUMPS

Mumps (Fig. 2), even more strikingly than mea-

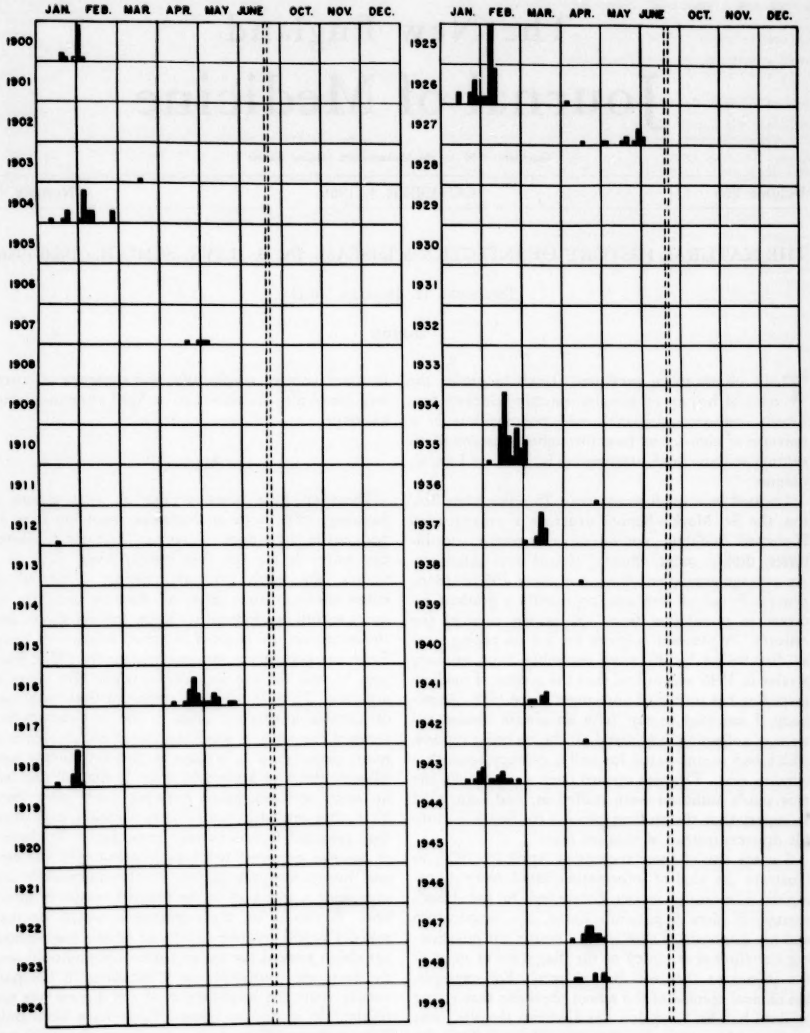

FIGURE 1. *Measles at St. Mark's School, 1900-1949.*

sles, has been deserting the ranks of this particular secondary school, and yet 60 per cent of the boys give a history of having had the disease before coming to boarding school. Only 20 cases are recorded in the past twenty years, and only 1 has occurred since January, 1950.

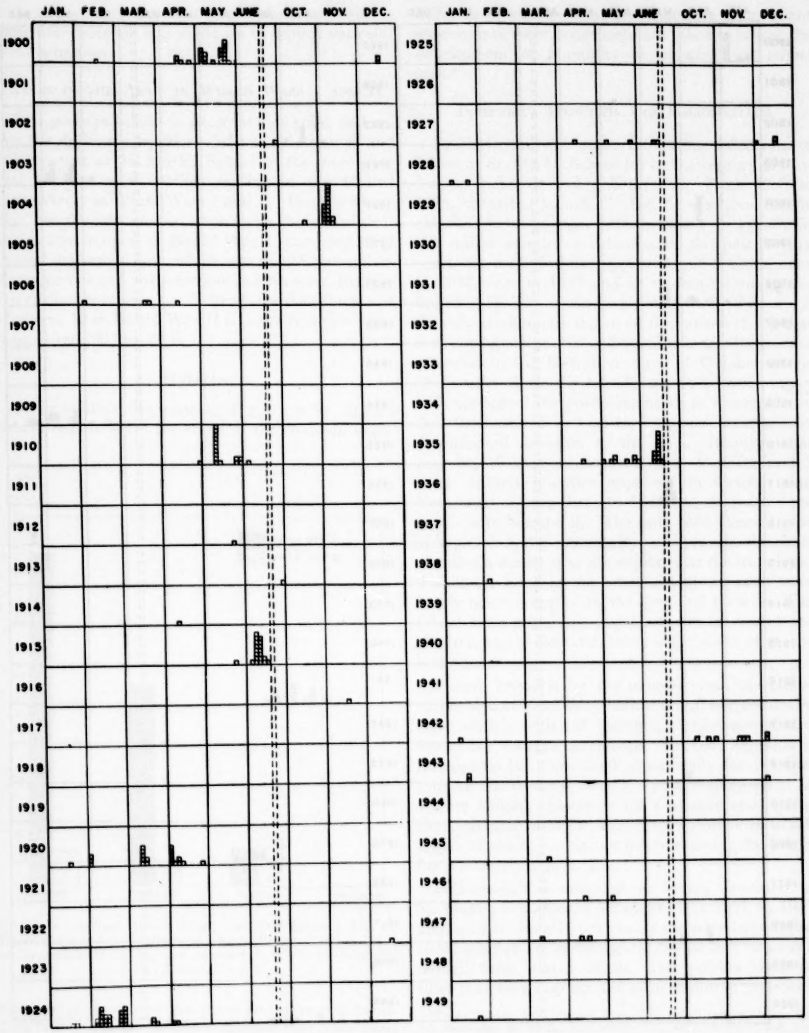

FIGURE 2. *Mumps at St. Mark's School, 1900-1949.*

CHICKEN POX

Chicken pox (Fig. 3) appears to behave about the same way from 1925 to 1950 as in earlier years; and the attack rate is only about 2 per cent per annum in each quarter of the century. Only 1 case has developed in the past six years. Yet 90 per cent of the

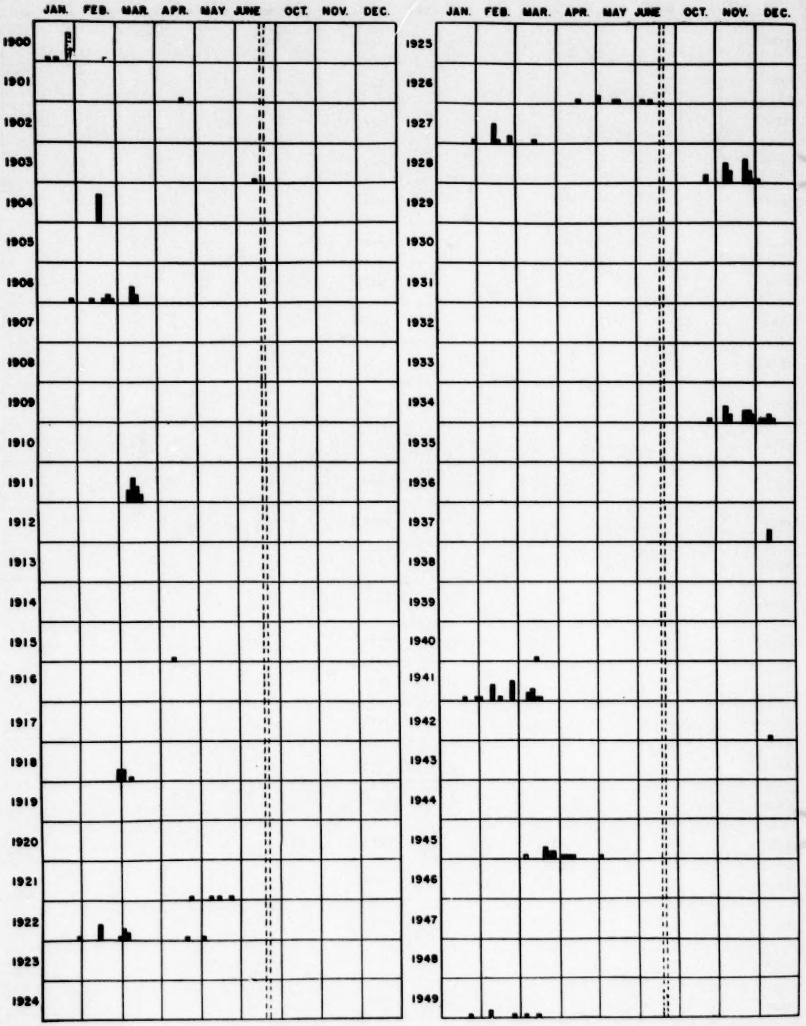

FIGURE 3. *Chicken Pox at St. Mark's School, 1900-1949.*

boys are recorded as immune. An interesting feature of the outbreak of 1941 is that the source case was one of herpes zoster, with distribution of the vesicles unilateral and limited to skin innervated by one of the intercostal nerves. Case 2 occurred in the roommate of the sentinel case. This boy had typical chicken

pox, as did another second-generation case. Thereafter, the epidemic was made up of typical varicelliform eruptions.

Rates in the Army in World Wars I and II

It is perhaps timely to pause at this point and relate the declining prevalence of measles, mumps and chicken pox at St. Mark's School to the more general experience of soldiers serving in the United States Army in World Wars I and II (Fig. 4). Here, also, measles and mumps were much more prevalent in the slower times of World War I than they were during the second war, which was one of movement. Rates for chicken pox were low in both wars. Rubella is a curious exception to the trend, for the attack rate of almost 10 in World War II is actually higher than it was from 1917 to 1919.

Rubella

As in military life, rubella (Fig. 5) at St. Mark's School fails to share the trend of the common exan-

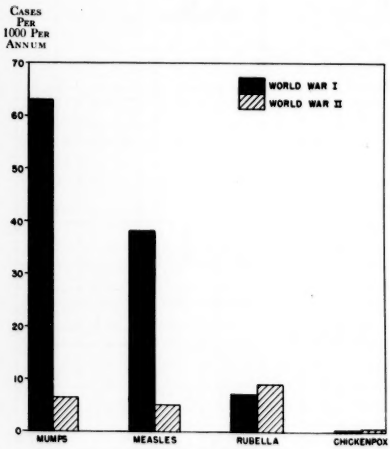

Figure 4. *Annual Attack Rates, per 1000 Soldiers, United States Army in the Continental United States, April 1, 1917, to December 31, 1919, and January 1, 1942, to June 30, 1945 (Source, Gordon[1]).*

thems to go down into the grade and nursery schools. This is the only one of the 4 diseases that have been compared to make its appearance more than twice in the 1950's. It has been back 9 times in the 1950's and as recently as March, 1956. In the spring of 1951 there were 21 cases; and in the spring and summer terms of 1956 there were 22 more cases before school closed for the long holiday. The findings indicate that rubella will continue to be an occasional infection of young adults and therefore of pregnant women until more active steps are taken to ensure the development of immunity at preschool or school ages.*

Infectious Hepatitis and Poliomyelitis

Probably the two most interesting infections to follow at St. Mark's School for half a century are infectious hepatitis and poliomyelitis. From 1900 to 1935 "catarrhal jaundice" (Fig. 6) was sporadically observed in more than half the years — usually in the colder months — whereas in the past twenty years the condition has appeared but 3 times, once in 1937, once in 1952 and in epidemic form in the fall of 1946. The sentinel case in 1946, by the way, is the only black square shown on the various charts that does not represent a schoolboy; in this case the patient recorded in the first three days of October is the chef's wife. Since she herself had no known contact with the school the possibility needs to be considered that the husband was an asymptomatic carrier who disseminated infection to the boys. However that may be, 19 cases of hepatitis with jaundice and 3 cases without jaundice appeared in October and November, twenty-three to forty-one days after the cook's wife became ill. The only other known case of hepatitis in the community not shown in the chart included a master who ate regularly at the school and 2 children living in the other half of the same two-family house occupied by the cook and his wife. The school master became jaundiced nineteen, and the children thirty-one and thirty-eight days after the first patient.

I leave hepatitis for the moment with the observation that it gives little indication of any epidemiologic kinship with the common droplet-spread diseases, like measles or mumps. Instead, hepatitis is revealed to have occurred sporadically for the first third of the century. Then, it nearly disappeared in a more sanitary era except for a massive and significant epidemic in 1945. This is an outbreak to which I wish to return — but not before showing the ledger for poliomyelitis (Fig. 7).

Poliomyelitis is recorded as having appeared in St. Mark's School on 3 occasions — in 1951, in 1947 and in 1936, when 10 per cent of the school developed either paralytic or nonparalytic disease in a two-week period; there was 1 death. The sudden block of cases that shows up against a succession of unbroken

*From January, 1950, through June, 1956, only 1 case of chicken pox (on September 26, 1953), 1 of mumps (on April 10, 1955) and 1 of infectious hepatitis (on October 3, 1951) have appeared at St. Mark's School. Measles has appeared twice — a single case on March 10, 1952, and an outbreak in the winter of 1955, with 3 cases on February 14 and 1 case on February 18, 1 on March 3 and 1 on March 9.

German measles, by contrast, has been introduced into the school 9 times since January, 1950, as follows: 21 cases in 1951, April 12, 13 and 29 (2), May 1, 2, 21 (2), 22, 23 (3), 24 and 25 and June 6, 7, 8, 9, 10, 11 and 15; 5 in 1952, February 3, 10, April 13, May 22 and October 1; 1 in 1955, April 14; and 22 in 1956, January 10, 28 and 30 and February 16, April 18, May 3, 7, 8, 21, 22, 26, 27, 28 and 29 (4) and June 1 (2), 3 (2) and 8.

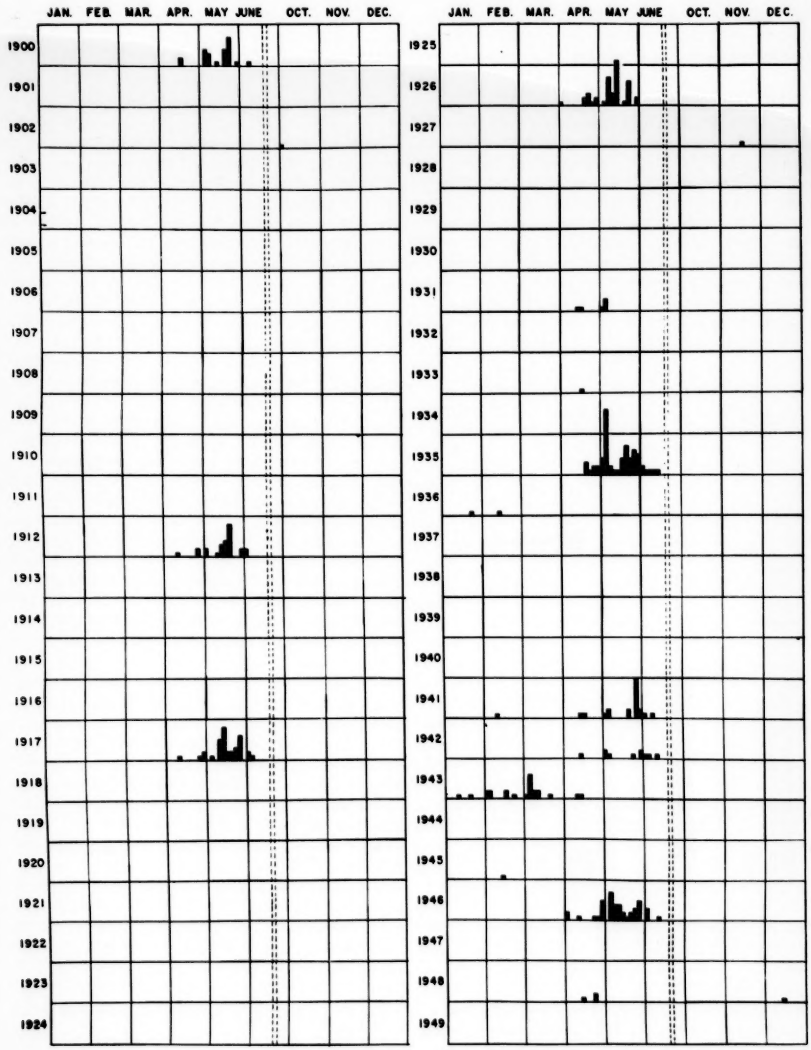

FIGURE 5. *Rubella at St. Mark's School, 1900-1949.*

white squares resembles nothing else that I have been able to discover in 10,000 morning reports except the outbreak of infectious hepatitis that has just been demonstrated. And, as with the hepatitis, what tenuous clues there are lead back to the kitchen personnel. I say tenuous, for no source case was ever

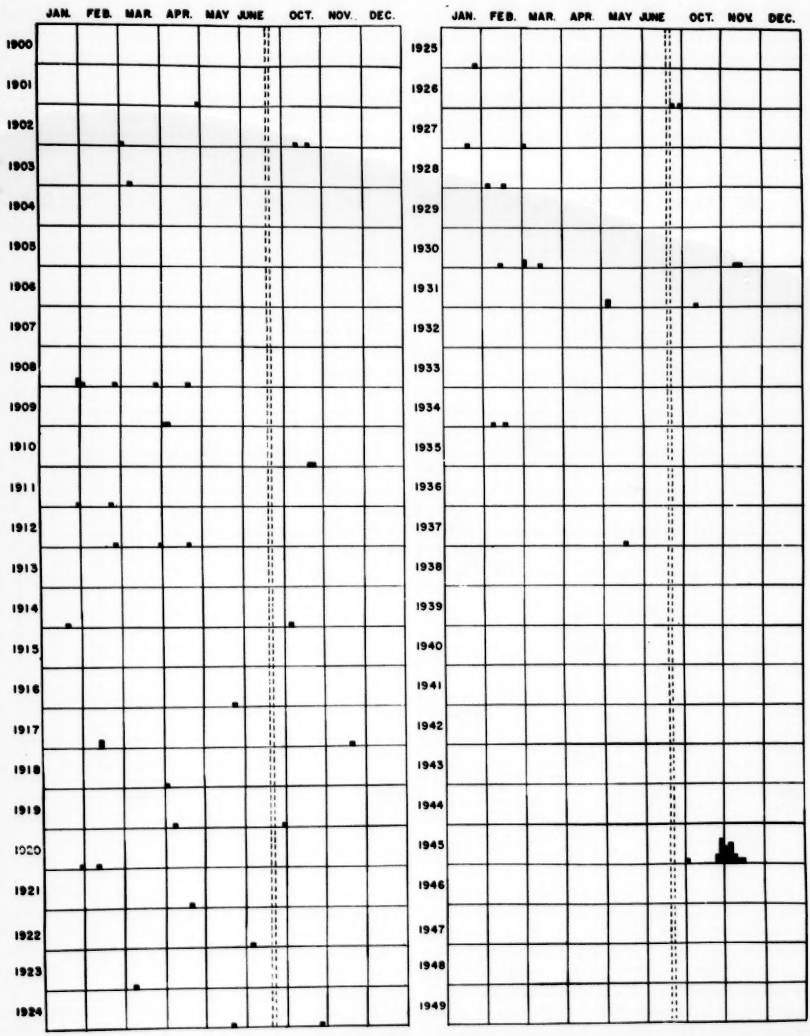

FIGURE 6. *Infectious Hepatitis at St. Mark's School, 1900-1949.*

identified. Nevertheless, a few facts and even a suspicion are worth recounting: 1936 was a very light year for poliomyelitis in Massachusetts whereas 1935 was the third largest year in the history of the State and cases were reported in nearby Marlborough in the fall. A sister of one of the Saint Mark's waitresses

residing in Marlborough was in the Massachusetts General Hospital during most of February, 1936, extensively paralyzed with Guillain–Barré disease. The waitress herself was out sick with a poorly defined illness on May 1 and 2. Incidentally, the month of May was the hottest recorded in weather annals since 1918. Temperatures were over 90°F. in early May, and I suspect that the Saint Mark's boys were having ice in their drinking water, for ice was regularly available in hot weather. Forty-pound cakes were frozen in copper cannisters, which had been sunk in the most dependent portion of the basement floor when the freezing plant was installed in 1917. I hope no one will misconstrue my statements as indicating that I have evidence that ice contaminated with sewage seepage caused poliomyelitis in 1936 and infectious hepatitis in 1946. All I know is that the chief engineer told me that the first thing that he had to supervise when he came to the school in the fall of 1935 was to break through an opening from the grill, on which the 40-pound blocks of ice could be tipped from their cannisters, so that the hose water — which also was used to fill the trays — could flush directly into the sewer running just below the basement floor.

But I digress from the more detailed description I had meant to give of the 1946 outbreak of infectious hepatitis (Fig. 9). Immediately when school opened on September 21, 1946, many cases of nausea, vomiting and diarrhea were observed — particularly among members of the football squad who had returned two days early. Incidentally, the top part of this figure can be ignored, for it merely shows enteritis in association with hepatitis at a boys' camp in Tennessee. The camp had to be closed down on July 10, and the jaundice later developed among boys long since returned home. The fact that fluorescin flushed down the toilets could be recovered in the spring water of the camp certainly has no bearing on the possibility that a similar mishap could have happened at the school. It is interesting, however, that all but 2 of the boys with hepatitis at Saint Mark's School had an antecedent episode of gastroenteritis; and there is a considerable similarity between the

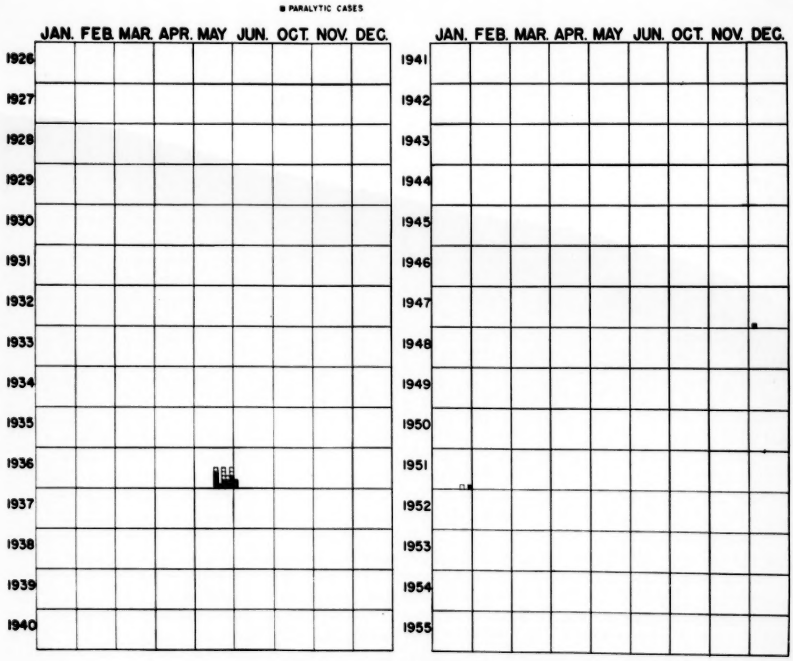

FIGURE 7. *Poliomyelitis at St. Mark's School, 1926-1955.*

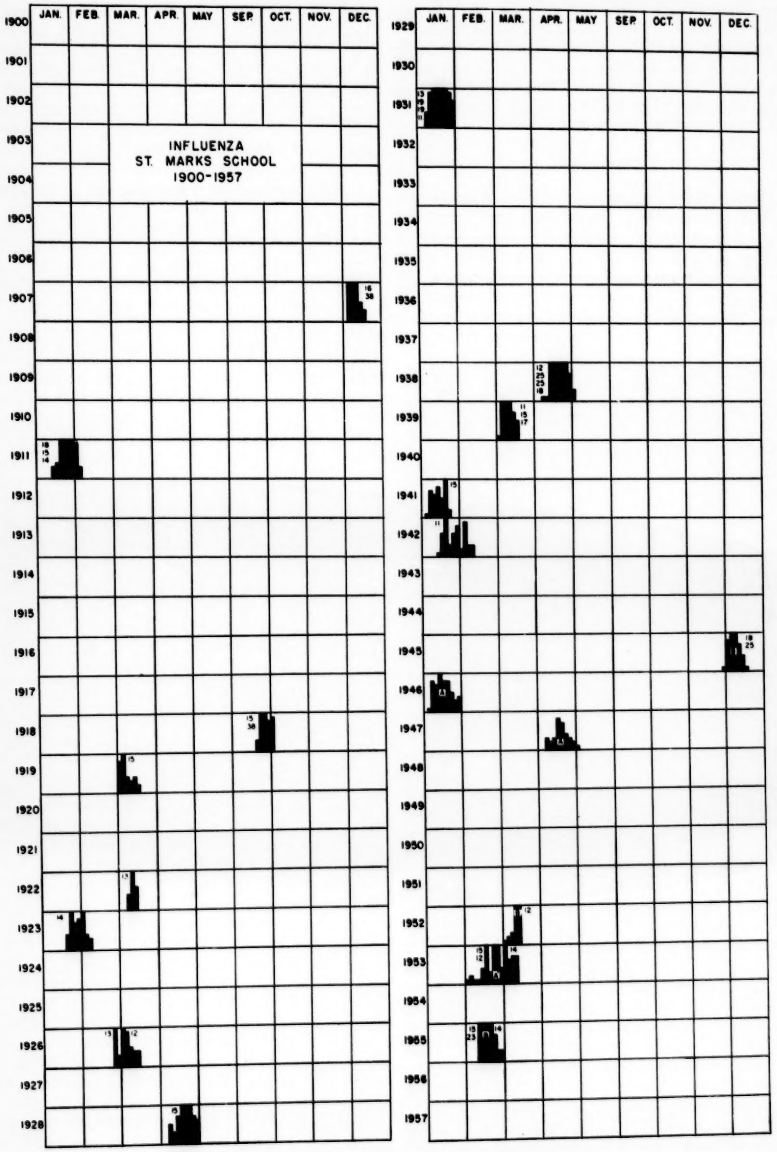

FIGURE 8. *Influenza at St. Mark's School, 1900-1957.*

two — or should I say four — epidemics. In any event the possibility warranted action and the Headmaster and I decided that the boys did not really need ice in their drinking water. The ancient freezing plant was ripped out and discarded; and thousands of dollars have since been spent on remodeling the kitchen facilities.

Influenza

Having gone from firm ground to quicksand I may as well keep wallowing on into the undifferentiated mass that is upper respiratory disease — colds, coughs, earaches, sinusitis and sore throats. From the confused welter one recurring theme can be disentangled with fair satisfaction — even though there is no pathognomonic exanthem, enanthem or glandular swelling. The disease is influenza, which is just about the only respiratory disease that comes sweeping through a small community like this and puts one quarter to one half of the inhabitants to bed within the space of perhaps three weeks (Fig. 8). Dr. Bacon, in 1918, was under no onus to search for the proper alphabetical label, but his repeated diagnoses of "grip-cold" within a matter of days suffice to stamp an epidemic as an epidemic. As a matter of fact, old Dr. Bacon would never deign to diagnose anything worse than "grip-cold" during the 8 outbreaks that he took care of in the first thirty years of the century — including the real "Spanish influenza" of 1918, which started its American march about August at Camp Devens and Greater Boston. School opened on September 18 and by September 21 the first 3 patients had reported to the infirmary — but for Dr. Bacon this was no flu or influenza; this was a "grip-cold." My own entry onto the epidemiologic scene was in 1946, just after influenza had turned the school upside down after the Thanksgiving recess of 1945 and again after the Christmas vacation a month later. Serologic tests were not made, but I have no hesitation about diagnosing the serologic type because the first outbreak corresponded with general experience for B and coincided precisely with a typed outbreak at Milton Academy. Likewise, the January outbreak coincided exactly with proved influenza A at Andover Academy. Thereafter, in the 1950's I have made my diagnoses like the doctors of old but have taken paired serums in to Max Finland and have come back with an A, 2 B's and an A′. The 1947 A is interesting in that infection predominated in the 40 new boys who had not been in school in January, 1946.

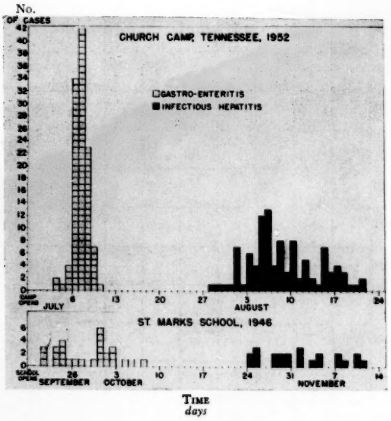

FIGURE 9. *Cases of Gastroenteritis and Infectious Hepatitis at Church Camp, Tennessee, in 1952 (after Tucker et al.[1]), Compared with Those at St. Mark's School in 1946.*

Discussion

As I take one more look at the records to summarize, certain trends are suggested for the common infectious diseases that are greatly fortified by attack rates observed in military installations during World Wars I and II. Mumps and measles are tending to drop down into grade and nursery school to a point that had already been reached by chicken pox.

German measles, on the other hand, remains a schoolboy problem — not that it carries an appreciable morbidity but because of the implication that the fact carries for the girls these boys will marry. Immunity against rubella, it is clear, needs a helping hand from many of you here. The virus needs to be captured and dispensed in the ice box even as vaccinia has been captured and is dispensed. An effective program would seem to be to convey infection to the grade-school or teen-age girl who has been so unfortunate as to escape it.

Infectious hepatitis, followed in this "closed community" for fifty-six years, has behaved like an enteric infection and, with improved sanitation, has practically disappeared from observation during the present decade. I refrain from commenting on poliomyelitis other than to say that the explosive outbreak of 1936 examined against a sporadic background resembles the explosive outbreak of hepatitis more closely than any other infection.

Finally, the data on influenza, open to question though they are, nonetheless give a useful index of the prevalence of such infections during the present century. In the future, such small universes should also provide a working sample of the larger community, and of parts of the nation, to maintain epidemic intelligence. I think that a boarding school like this might be well suited to help confirm the long-term effectiveness of a vaccine that has already been submitted to provisional tests for safety and effectiveness.

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CALCIFIED LIVER METASTASES*

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CALCIFICATION in the right upper quadrant may lie in the kidney, adrenal gland, gall bladder, liver or retroperitoneal area. Kidney tumors and tuberculosis of the kidney do show calcification. By means of positioning or, if necessary, pyelography, one can determine whether calcification lies within the kidney. Cholecystography is helpful in locating the margin of the liver, and in differentiating gallbladder calcification. Liver calcification is quite rare[1]; echinococcus disease shows ringlike calcification in the cyst walls; in tuberculosis the calcification is miliary; calcification in hemangiomas may be streaky[2] or may resemble phleboliths. Calcification in metastases is referred to rarely in the literature; 3 cases of feathery calcification in the liver due to metastases, all from the colon, were recently encountered; 2 of these were diagnosed before operation. Sangster[3] has reported a case of carcinoma of the rectum in which a thirty-three-year-old pregnant woman showed calcification in the primary mucoid carcinoma. "There is a gelatinous carcinoma of the bowel . . . and white gritty material in the substance of the growth." Dr. Edith Sproul,[4] pathologist at the Delafield Hospital in New York City, states that when calcium is found in abdominal lymph nodes involved with metastatic carcinoma, she considers this suggestive evidence that the primary neoplasm is in the rectum or in the sigmoid. Recently, calcification in liver metastases from an adenocarcinoma of the sigmoid that had been removed six years previously was observed.[5]

Case Report

CASE 1. E. S. (P. H. 62-78-30), a 41-year-old woman, was admitted to the hospital because of abdominal pain in the right upper quadrant of 4 months' duration. There was a history of cancer in 4 members of her mother's family.

Physical examination showed the liver to be large and tender. Significant laboratory findings were slight anemia, elevated sedimentation rate, a negative cephalin flocculation and a negative echinococcus skin test, a faint trace of bilirubin and an alkaline phosphatase of 13.3 Bodansky units.

X-ray studies disclosed a normal intravenous pyelogram, negative barium-enema study, normal gastrointestinal series and normal film of the chest. A tender mass was noted in the region of the liver on fluoroscopy; films of the right upper quadrant of the abdomen showed small particles of calcification in the region of the right lobe of the liver, the significance of which was unknown (this was the 1st case).

At exploratory celiotomy, a hard nodular growth was found in the liver; some of the calcified tissue could be felt. Biopsy was reported as follows:

> There are scattered epithelial cells forming rounded, irregular, glandlike structures. The walls are formed by several layers of cells that vary greatly in size and shape, but tend to be columnar.
>
> The diagnosis is carcinoma of the liver following carcinoma of unknown origin; the most probable source is the gastrointestinal tract.

Bleeding by rectum and evidence of partial intestinal obstruction later developed. The patient died 6 months after exploration and 9 months after the calcification was noted by x-ray examination. At autopsy carcinoma of the sigmoid, with metastases to the liver, lungs and lymph nodes, was found. Calcium was observed both in the primary tumor and in the metastases in the liver. The liver weighed 6300 gm. Massive tumor nodules with central umbilication were noted. These were composed of firm, fibrous tissue with calcification in the central portions. Liver sections showed extensive necrosis, with calcium salts deposited in the necrotic material; calcium was abundant and present chiefly in the necrotic débris. At the proximal end of the sigmoid, an oval tumor mass was seen projecting into the lumen and extending through the wall to the peritoneal surface. On microscopical section considerable necrosis was observed in

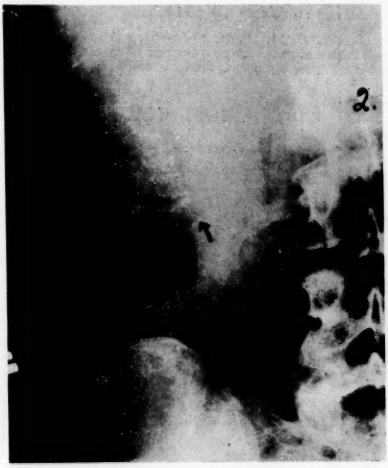

FIGURE 1. *Roentgenogram, Showing Finely Granular Calcification in the Right Upper Quadrant opposite the Second Lumbar Vertebra.*

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the tumor, with calcification in the necrotic areas. The lymph nodes in the retroperitoneal area and in the mesentery showed hard, white, gritty material within them.

The terminal event was perforation of the colonic carcinoma, with peritonitis.

CASE 2. D. S. (P.H. 76-83-11), a 21-year-old woman, was admitted to the hospital with a history of right-flank pain and fever of 3 weeks' duration and a loss of 11.3 kg. (25 pounds) in weight since delivery of her 1st child 6 months before. She had had diarrhea for 3 months and had passed some blood by rectum.

Physical examination revealed a slightly jaundiced woman. There was a tenderness in the right upper quadrant of the abdomen and a large, hard, nodular liver. Significant laboratory findings were anemia, a negative cephalin flocculation, an alkaline phosphatase of 31.5 Bodansky units, a bilirubin of 2.4 mg. per 100 ml., a negative urinalysis and a positive stool guaiac test, with no parasites in the stool.

X-ray studies showed a normal chest, a low right kidney on an intravenous pyelogram, a large liver and faint punctate calcifications in the right upper quadrant, at first thought to be gallstones but later diagnosed as calcification within the liver substance. The x-ray report read as follows:

> The small punctate shadows of calcium density superimposed upon the liver are not due to gallstones but suggest calcium deposits within the liver. The possibility of parasites is mentioned as a cause. However, a previous case with similar small calcium shadows superimposed upon the liver proved to be a cancer of the liver.

An exploratory celiotomy was done. Large, lobulated, grayish-white masses were found in the liver. No further exploration was done. The liver biopsy showed that the liver tissue was "largely replaced by a tumor, made up of relatively well differentiated mucous glands lined by tall columnar cells, that closely resembles tumors derived from the large bowel." The diagnosis was carcinoma of the liver following carcinoma of (colon?). The patient died at home, and no autopsy was performed.

CASE 3. C. M. (P. H. 15-55-66), a 51-year-old woman, was admitted to the hospital because of epigastric discomfort after meals for 8 months. She gave a history of an operation at another hospital for diverticulitis of the colon 2½ years previously.

On physical examination a large, hard nodular liver was found. In the laboratory studies, anemia, an elevated sedimentation rate, an alkaline phosphatase of 8.9 Bodansky units, a bilirubin of 0.2 mg. per 100 ml. and a negative cephalin flocculation were noteworthy.

X-ray examinations revealed a normal gall bladder, normal upper gastrointestinal tract and normal colon, an elevated right leaf of the diaphragm and a faint feathery calcification (Fig. 1) in the right upper quadrant. The question of liver metastases from carcinoma of the colon was suggested by the radiologist; the patient's surgeon reported that he had removed a carcinoma of the sigmoid, with lymphatic metastases, 2½ years previously. She was re-explored by him at another hospital.

There was free fluid in the abdomen and many carcinomatous deposits in the liver. No biopsy was done. She died a few months later; no autopsy was performed.

SUMMARY

Three cases of calcification in liver metastases are reported. The primary tumor in 2 of these cases was proved to be in the sigmoid; in the other, according to the history and pathological report, the primary lesion was probably in the colon although this was never proved. It is noteworthy that in this small series the calcification in the liver was very fine and was quite difficult to see on x-ray examination.

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HOST INFLUENCE ON UPPER RESPIRATORY FLORA

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THE study of the spread of bacterial pathogens in a free-living human population presents obvious difficulties. We have considered that a practical method was, first, to determine some common endemic pathogens in a given population and, secondly, to observe the incidence and concentration of these organisms in the members of a group of families over a given period.

If an organism, once introduced into the family group, were found to be present in approximately equal quantities and with equal frequency in all members, we should assume that no host factors influenced colonization. If, however, the organism, once introduced, were found consistently to be present more frequently and in larger quantities in certain members, and less frequently or not at all in others, we might assume that some selective host factors were at work.

We have chosen throat and nose flora for observation because the cultures are easily taken, even by a member of the family group, the organisms are readily identifiable by simple bacteriologic methods and it can be assumed that respiratory flora is freely exchanged in the close associations of normal family life.

This work was done on a small group of families from six towns in the Nashoba Health District, a rural area in central Massachusetts. Preliminary observations showed that the common respiratory pathogens present were the hemolytic streptococcus, *Haemophilus influenzae* and the pneumococcus.

Also included in the study was *H. haemolyticus*, which, it is assumed, has no pathogenic significance. No attempt to type any strains was made.

Families were selected at random. Criteria for selection included the presence of both parents and

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at least two children, preferably of preschool or young school age, reasonable intelligence, so that family members could take and mark swabs when necessary, and willingness to co-operate.

In this report no attempt has been made to correlate presence of the pathogens with clinical data. Observations have been confined to the ability or lack of ability of the organism to grow in a given host. It may be stated, however, that all the subjects were essentially healthy throughout the period of observation. They went to their family doctors when they were sick, and otherwise received no particular medical supervision. Ten general practitioners were involved, — 9 besides one of us, — and these 9 have generously permitted us to inspect their records. None of the persons studied were given antibiotic treatment except for specific clinical reasons, and, as would be expected, these reasons occurred chiefly in the children two to ten years of age.

TABLE 1. *Summary of the Distribution of the Four Organisms.*

HOSTS	BETA-HEMOLYTIC STREPTOCOCCI	*H. influenzae*	PNEUMOCOCCI	*H. haemolyticus*
Exposed people (organism present in family group)	153	201	195	191
Number who had organism	73	184	129	165
Number who did not have organism	80	17	66	26
Adults*	48	13	49	15
Children†	32	4	17	11
Exposed families (organism present in household)	28	38	37	36
Families in which every member had organism	0	27	8	22
Families in which 1 or more members did not have organism	28	11	29	14

*Over 16 yr.
†15 yr. & under.

HISTORICAL REVIEW

The literature on respiratory flora is immense, and we mention only a few writers whose findings seem especially pertinent to our work.

Bloomfield[1] found that when foreign particles and bacteria were introduced into the mouth, they were quickly carried back toward the esophagus. New bacteria colonized in the mucous membranes only when conditions were suitable for growth; on the other hand, native flora could not be removed by washing.

Badger et al.[2] studied the spread of nonbacterial respiratory diseases in a group of families. They began with 5 families in 1947, and had 61 by December 31, 1950. They found that preschool and school children brought home twice as many colds as fathers; young children in kindergarten brought home the most. Once a cold was introduced into the home, all members were considered equally at risk. Secondary cases occurred less often in the father than in the mother. A gradual immunity developed with age, apart from experience.

TABLE 2. *Carrier Rates for Family 4.**

MEMBER OF FAMILY	RATE OF BETA-HEMOLYTIC STREPTOCOCCUS		RATE OF *H. influenzae*		RATE OF PNEUMOCOCCUS		RATE OF *H. haemolyticus*	
	THROAT	NOSE	THROAT	NOSE	THROAT	NOSE	THROAT	NOSE
Father	0	0	0	0	0	0	0.08	0
Mother	0	0	0.07	0	0	0	0	0
Peter (9 yr.)	0	0	0.31	0.15	0	0.07	0.23	0
Preschool children:								
Danny (5 yr.; foster child.)	1.69	0	0.23	0	0	0.07	0.46	0
Lisa (5 yr.)	1.07	0	0.31	0.15	0	0.38	0.31	0
Sarah (1 yr.)	0	0	0.38	0	0.07	0.92	0.46	0

*Studied for 1 yr.; 13 cultures.

Dudley[3] observed the spread of diphtheria in a boys' school for a period of thirteen years, starting in 1919. Experience with the bacillus during an epidemic produced Schick immunity in those who were not clinically ill. Decreasing carrier rates paralleled increasing seniority in the school. With artificial immunization in 1928, a sharp drop in case rate and also in carrier rate occurred.

TABLE 3. *Carrier Rates for Family 22.**

MEMBER OF FAMILY	RATE OF BETA-HEMOLYTIC STREPTOCOCCUS		RATE OF *H. influenzae*		RATE OF PNEUMOCOCCUS		RATE OF *H. haemolyticus*	
	THROAT	NOSE	THROAT	NOSE	THROAT	NOSE	THROAT	NOSE
Father	0	0	0.17	0	0.08	0	0.25	0
Mother	0	0	0.18	0	0	0	0.23	0
F.W., Jr. (14 yr.)	0.41	0	0.33	0	0	0	0.30	0
Betty (12 yr.)	0.57	0	0.70	0	0.04	0	0.30	0
Nancy (8 yr.)†	1.26	0.13	0.22	0	0.04	0.09	0.44	0
Preschool children:								
David (4 yr.)	1.21	0	0.38	0	0.25	0.54	0.21	0
Sarah (1½ yr.)	0.42	0	0.54	0	0	0.21	0.63	0
Other adults in household:								
Mrs. E.	0	0	0.26	0	0	0	0.21	0
Cook J.	0	0	0.19	0	0.10	0	0.19	0

*Studied for 2 yr.; 23 cultures.
†Acute nephritis developed during study.

Fothergill and Wright[4] studied *H. influenzae* meningitis, and found that there was an inverse relation between its incidence and the bactericidal power of the blood. Babies between three months and three years were highly susceptible, and their blood showed very low bactericidal power for the organism; with age, bactericidal power and resistance increased.

TABLE 4. *Carrier Rates for Family 14.**

MEMBER OF FAMILY	RATE OF BETA-HEMOLYTIC STREPTOCOCCUS		RATE OF *H. influenzae*		RATE OF PNEUMOCOCCUS		RATE OF *H. haemolyticus*	
	THROAT	NOSE	THROAT	NOSE	THROAT	NOSE	THROAT	NOSE
Father	0.56	0.04	0.36	0	0	0	0.64	0
Mother	0	0	0.37	0	0.13	0	0.25	0
Virg. (12 yr.)	0.24	0.29	0.44	0	0.08	0.21	0.84	0
Natalie (10 yr.)	0	0.13	0.46	0	0.04	0.13	1.04	0
Nancy (6 yr.)	0.32	0.17	0.44	0	0	0	0.76	0
Preschool children:								
Chris. (4 yr.)	0.13	0	0.28	0	0	0.21	0.24	0
John (2 yr.)	0.33	0.04	0.30	0	0	0.23	0.26	0

*Studied for 2 yr.; 25 cultures.

Powers and Boisvert[5] observed the different clinical manifestations of streptococcal disease according to age. Children under three years rarely had scarlet fever, acute tonsillitis or rheumatic fever; these acute

TABLE 5. *Carrier Rates for Family 13.**

MEMBER OF FAMILY	RATE OF BETA-HEMOLYTIC STREPTOCOCCUS		RATE OF *H. influenzae*		RATE OF PNEUMOCOCCUS		RATE OF *H. haemolyticus*	
	THROAT	NOSE	THROAT	NOSE	THROAT	NOSE	THROAT	NOSE
Father	0	0	0	0	0	0	1.21	0
Mother	0.21	0	1.07	0.21	0.43	0.43	0.43	0
Richard (12 yr.)	1.07	0	0.47	0.20	0.20	0.27	0.94	0
Francis (9 yr.)	1.00	0.14	0.36	0	0.07	0.21	0.72	0
Linda (7 yr.)	1.28	1.43	0.14	0.14	0	0	1.00	0
Marty (6 yr.)	0.64	0.79	0.50	0	0.14	0.14	0.72	0
Preschool children:								
David (1-2 yr.)	0.21	0	0.29	0.43	0.44	1.29	1.36	0.21
Anne (0-1 yr.)	0	0	0.20	0.13	0.13	1.40	0.33	0

*Studied for 1 yr.; 15 cultures.

reactions occurred frequently from three to nine or ten years of age and decreased with increasing years.

Schwentker, Janney and Gordon[6] studied the distribution of the hemolytic streptococcus in Roumanian villages. They found a definite age curve of incidence. The highest carrier rate occurred between five and fourteen years; a lower rate occurred in the group from fifteen to nineteen years of age, and the lowest in children under five years. This carrier rate was measured by means of throat swabs once a month on a miscellaneous group of normal persons comprising about 10 per cent of the population; the group swabbed differed each month.

METHODS

In the present study repeated monthly throat and nose cultures were taken on the same group of people for a period covering twenty-one months. Thirty-eight families were observed; they stayed with us for varying lengths of time, from five to twenty-one months. The entire household group was swabbed at each visit, or within one twenty-four-hour period. Swabs were taken either by the investigators or by the older members of the family. After these members were trained in the method, we found no difference in quality of cultures.

TABLE 6. *Distribution, by Ages, of Cultures Taken.**

AGE	NO. OF PEOPLE	NO. OF CULTURES
yr.		
0- 1	11	99
1- 2	20	170
2- 3	24	199
3- 4	21	164
4- 5	19	179
5- 6	18	146
6- 7	18	156
7- 8	16	163
8-10	18	207
10-12	16	205
12-15	10	127
15-25	4	56
25-35	50	659
>35†	32	541

*May include 1 individual 2 or 3 times, if period of study covered more than 1 of his calendar yr. of life; child 6 mo. old at 1st swabbing & 18 mo. at last would be tabulated in 2 separate periods — 0-1 & 1-2 yr.

†Of these, 1 was 57, & another 86 yr. old; remainder in 35-45-yr. bracket.

"Throat" meant one good swabbing over oropharynx and tonsils. "Nose" meant one swab for both outer nares. Swabs were transported to the laboratory and planted as quickly as possible; we found that five hours was the maximum time they could be kept without deterioration. Fresh horse-blood agar plates were used; one plate was allotted for each person, — three quarters of the area for throat, and one quarter for the nose. Streaking was done so as to obtain optimum distribution of colonies.

Plates were incubated at 35°C. and read within twenty-four hours. Identification of the main divisions of bacteria was done by ordinary bacteriologic methods only. This paper is concerned with 4 classes of organisms, and they were identified by the following simple criteria:

Beta-hemolytic streptococci: presence of beta hemolysis, with positive stab subculture, and gram stain.

H. influenzae: colony type, odor (at times) and gram stain.

Pneumococcus: colony type, solubility in 1 per cent Dreft and gram stain.

H. haemolyticus: presence of hemolysis, colony type and gram stain.

As has been said, no attempt was made to group or type any organisms. Distinction between *H. influenzae* and *H. haemolyticus* was made solely on the presence or absence of hemolysis; in other words, an occasional strain of nonhemolytic *H. parapertussis* may have been included under *H. influenzae*. Also, no distinction has been made in the present summary between capsulated and noncapsulated *H. influenzae*.

Results were recorded on simple charts; one chart was used for each monthly swabbing of each family, the entire family picture being described on one chart for each visit.

We measured the intensity of colonization by assigning one of 4 values to each culture for each organism:

0 — none.
1 — a few colonies (4 or less).
2 — anything between a few and a covered plate.
3 — abundant (plate more or less covered).

These figures were recorded for each culture for each person, and added at the end of the period of observation. This sum, divided by the total number of cultures for that person, gave us our "rate of colonization," or index. This same index has been used in all the calculations recorded below.

In the measurement of rates for different age groups an average was figured for the total number of individuals falling in that age; the tables and graphs use these averages. When an individual fell into two age groups — that is, when his birthday came in the middle of the experiment and more than three cultures fell on either side of that birthday these results were divided into the two appropriate categories.

Results

Of the 38 families studied the number of visits made per family was as follows: maximum, 25; minimum, 6; and average 15. The number of people per family was as follows; maximum, 9; minimum, 4; and average, 5.3. The geographic distribution of the families was as follows: Littleton, 22; Harvard, 8; Groton, 2; Ayer, 4; Boxboro, 1; and Lunenburg, 1. Among the 201 subjects of the study 3071 cultures (throat and nose both) were made. The period of the study was September, 1953, to July 1, 1955.

A summary of the distribution of the four organisms is presented in Table 1. A definite difference in distribution between the species can be observed. *H. influenzae* was present in all 38 families, and in all members of 27 of those 38 families. Hemolytic

TABLE 7. *Rate of Colonization by Years, When Organism Is Present in a Family Group (See Figures 1-4).**

Age	Colonies of Beta-Hemolytic Streptococcus		Colonies of *H. influenzae*		Colonies of Pneumococci		Colonies of *H. haemolyticus*	
yr.	THROAT	NOSE	THROAT	NOSE	THROAT	NOSE	THROAT	NOSE
0- 1	0.05	0	0.46	0.17	0.13	0.62	0.37	0.04
1- 2	0.15	0	0.66	0.23	0.14	0.54	0.40	0.01
2- 3	0.26	0.02	0.58	0.17	0.13	0.47	0.35	0
3- 4	0.43	0.05	0.67	0.43	0.06	0.47	0.24	0
4- 5	0.38	0.01	0.71	0.20	0.18	0.55	0.60	0
5- 6	0.56	0.04	0.80	0.39	0.09	0.43	0.41	0
6- 7	0.46	0.20	0.57	0.12	0.23	0.48	0.50	0
7- 8	0.27	0.13	0.38	0.21	0.19	0.33	0.33	0
8-10	0.38	0.03	0.49	0.08	0.25	0.28	0.49	0
10-12	0.21	0.06	0.39	0.09	0.08	0.11	0.49	0
12-15	0.21	0	0.37	0.02	0.07	0.14	0.48	0
15-25	0.23	0	0.21	0	0.10	0.05	0.36	0
25-35	0.07	0.01	0.33	0.02	0.07	0.04	0.38	0
>35	0.12	0.02	0.32	0	0.07	0.03	0.51	0

*Figures are sum of total concentration of organisms found, divided by number of cultures taken.

streptococci, on the other hand, were present in only 28 of the 38 families, and in none of these was it universally present. Pneumococci and *H. haemolyticus* occupied intermediate positions in the ability to be distributed. If we count individuals, we find that 184 of the 201 people exposed to *H. influenzae* carried it at some time or other, whereas of the 153 people exposed to hemolytic streptococci, only 73 carried it at any time, and 80 never had it, although we know that they were exposed in their family groups. Again, pneumococci and *H. haemolyticus* occupied an intermediate position in this pattern of distribution.

Tables 2-5 are typical charts summarizing the distribution of each organism studied in our household groups. Most of our families presented a picture like that found in families 4 and 22 (Tables 2 and 3) — that is, the adults did not carry pathogens as abundantly as the children. A few presented pictures like that in families 13 and 14 (Tables 4 and 5), in which 1 parent also carried pathogens in abundance. In surveying our family records, we found that 1 (family 7) showed an almost complete lack of pathogens

throughout the study. This family lived in the center of the village community, had two children in public school (ages ten and thirteen) and a young baby. The members of the family had a number of illnesses during the year, but at no time carried any significant number of pathogens.

All the other families carried bacterial pathogens in fair abundance at some time during the study. Several individuals, although repeatedly exposed to the hemolytic streptococcus in great abundance in their family groups, showed remarkable antibacterial resistance by never harboring it at any culture.

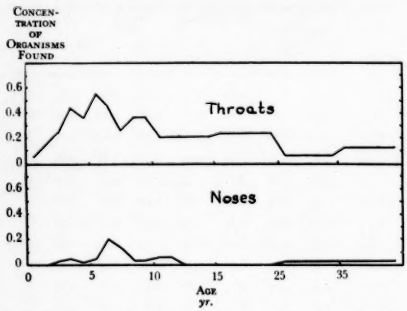

FIGURE 1. *Age-Distribution Curves for Beta-Hemolytic Streptococcus.*

The age distribution of the cultures is shown in Table 6. In general the hemolytic streptococcus was found most frequently in the throats of children between three and nine years of age (Table 7). A rounded age-distribution curve can be constructed from our data, taking into consideration all the exposed individuals, but none outside households where the organism was known to exist (Fig. 1). As can be seen, babies in the first year of life were seldom found to harbor the organism. The incidence rose sharply year by year to a peak at five or six years, with a slow decline thereafter. Adults were free of the organism with the exception of the chronic carriers and certain others who had it at times of acute illness. Streptococci were found in noses in lesser quantities and with diminished frequency, but the same type of curve is indicated.

H. influenzae shows the same type of distribution by age with the exception that babies and older people tend to carry it, too, although less frequently and less heavily than the children five to six years old. Adults rarely carry it in the nose. Its almost universal presence in old and young in all our families raises difficulties in the study of its clinical significance. Our data as presented do not indicate whether or not the strains were capsulated and, therefore, presumably virulent; it is believed from casual observation, however, that the mucoid, capsulated forms were almost invariably found in young children (Table 7 and Fig. 2).

The pneumococcus showed little significant variation by age in the throat, but it was most common for the baby of the family to carry it in his nose. In fact, a veritable age precipice was found regarding the pneumococcus in noses, this, it will be recalled, referring only to the outer nares (Table 7 and Fig. 3).

H. haemolyticus was found about equally in all age groups in throats, but virtually never in any noses (Table 7 and Fig. 4).

Discussion

Host factors suggested by our findings include age influence, local tissue resistance and individual susceptibility and resistance not yet explained.

It seems likely that babies under one year share with their mothers some developed resistance to the beta-hemolytic streptococcus. This resistance is particularly startling in such groups as family 13, in

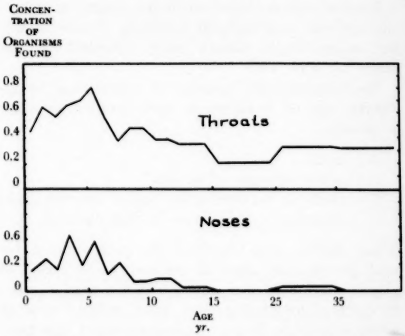

FIGURE 2. *Age-Distribution Curves for* H. influenzae.

which 8 people were crowded into a 4-room house, where the 5 older children, persistent carriers of streptococcus, all shared in the care of the baby. It was impossible that she was not "exposed" to the organism. Likewise, her next older sibling, a child under two years of age, carried streptococci only sparsely. This same situation was observed in family 22; the baby, S., did not carry the organism during her first year under observation, when she was between one and two years old. During the second winter, however, when she was between two and three, she carried it several times.

The exposed children carried more and more streptococci until they reached the peak at five to six years of age. The carrier rate remained high through

the period from six to ten years, but in this period, or shortly thereafter, they seemed to divide into the obvious carriers and those in whom antibacterial resistance developed.

Some of the adults seem to carry the organism most of the time and yet are never sick. Does this represent more "resistance" than that obtaining for those who throw off the organism altogether, even though repeatedly exposed — such as the wives in families 14 and 31, or the husband in family 13, who were never found to harbor the organism? Host factors that need further elucidation are suggested.

Our data suggest that to a certain extent the same situation exists for *H. influenzae;* the age curve is much less pronounced, however. The situation with the pneumococcus is entirely different; in throats the curve from six to ten years is very low. Yet in noses the picture is definitely meaningful. Why does the baby carry pneumococcus in the nose and not in the throat? A local tissue factor is suggested. Possibly, the fact that the nose is lined with columnar ciliated epithelial cells similar to those in the lower respiratory tract, whereas the oropharynx is lined with stratified squamous cells, has some bearing on the difference in type of bacteria that can grow in the two areas. Possibly, also, some inhibitory factor in adult noses is lacking in the noses of young children and babies.

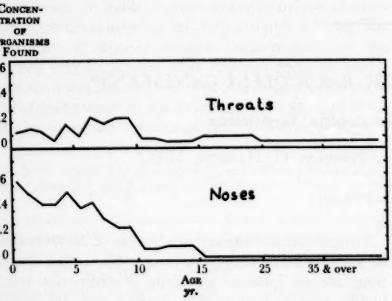

FIGURE 3. *Age-Distribution Curves for Pneumococcus.*

Clinical correlation of the presence or absence of the three pathogens would be a fascinating study. Unfortunately, only some of the families are under sufficiently frequent and unified medical observation. It would be difficult to gather statistically significant numbers of comparable situations. However, as with every family doctor, individuals stand out in the mind and raise interesting questions. There was R. H., a three-year-old girl in family 17, who had frequent long-drawn-out "colds" that became purulent and responded promptly to oxytetracycline. During the year of these infections she carried no hemolytic streptococci. In the following year, at four years of age, she was well all winter but was found to be constantly and fairly heavily colonized by streptococci in the throat. The oldest member of the study group, an eighty-six-year-old woman in excellent health, also in family 17, never at any time was found to harbor any of the study organisms, though she was repeatedly exposed to them in large numbers. There were also the three doctors in the group, in families 16, 17 and 22, who, presumably, were frequently exposed to virulent streptococci. One was found lightly colonized on one culture. The 5

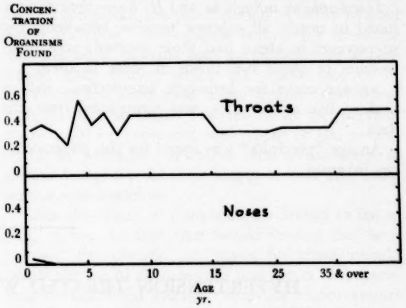

FIGURE 4. *Age-Distribution Curves for* H. haemolyticus.

children of a mother whose husband was, for a time, a chronic streptococcus carrier, had repeated streptococcal infections, including scarlet fever, but the mother never harbored the organism, although she herself never received antibiotics (family 14). Is this a more important form of host resistance than that of her husband, who harbored the organism but was not sick?

During the two years of the study there was 1 child, a girl nine or ten years of age in family 22, who carried hemolytic streptococci off and on for twenty-one months (along with her siblings) and appeared well throughout the time. At the end of the period of study, however, acute nephritis developed. Another child not in the study but under the care of one of us (H.S.H.) contracted acute rheumatic fever. She had had previous illness not medically observed. Throat cultures at the time the rheumatic fever was discovered were negative for streptococci. Throat cultures of a sibling and of a neighbor child who was a constant companion of the family were positive for hemolytic streptococci at this time. These cases are too few in number for conclusions of any sort. They do, however, suggest the kind of problems that might be handled with more extensive work.

Our data indicate that the most marked host influence occurred with the organism known to be

most pathogenic — the hemolytic streptococcus — and that practically no host influence occurred with an organism that is not considered to be pathogenic — *H. haemolyticus;* an intermediate position was occupied by *H. influenzae* and the pneumococcus, organisms whose pathogenicity, when they are resident in the upper respiratory tract, is variable.

Summary

Three thousand and seventy-one throat and nose cultures on 201 people divided into 38 family groups were studied for a period of twenty-one months.

Haemophilus influenzae and *H. haemolyticus* were found in nearly all exposed persons, beta-hemolytic streptococci in about half those exposed, and pneumococci in about two thirds of those exposed.

An age curve for hemolytic streptococci, with a peak at five to six years, was constructed from the data.

An age "precipice" was found for the pneumococcus in noses.

We are indebted to Dr. Kenneth I. E. Macleod, former director of the Nashoba Associated Boards of Health, and his predecessor, Dr. Sidney Cobb. We are also indebted to Dr. C. C. Li, of the Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, for our method of analysis. Valuable advice was given by Dr. Johannes Ipsen, Jr., director of the Institute of Laboratories, Massachusetts Department of Public Health. Without the co-operation of the family physicians in the towns and of the families themselves this study would obviously have been impossible.

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HYPERTENSION TREATED WITH *RAUWOLFIA CANESCENS**

A Comparison with *Rauwolfia Serpentina*

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THE widespread acceptance of the preparations of *Rauwolfia serpentina* for the treatment of patients with arterial hypertension and mental disorders has stimulated further investigation regarding other forms of Rauwolfia. One of these species, *R. canescens,* has been reported by Chakravarti[1] to show greater adrenolytic activity with less hypnotic effect than *R. serpentina.* This effect was attributed by Mukherjee[2] to a crystalline alkaloid, rauwolscine, which was isolated in 1941[3] and was thought to be the active principle of *R. canescens.* Since then the well known alkaloid, reserpine, has been isolated from *R. canescens* by Klohs and his co-workers.[4] In addition, other chemical analyses of *R. canescens* have shown that a number of different alkaloids are present, some being quite similar in their pharmacologic activity to reserpine.[5-8] Chief of these new alkaloids is 11-desmethoxyreserpine. Thus, at least three distinct alkaloids that possess hypotensive activity are present in *R. canescens.*

Several factors may restrict the use of *R. serpentina* in the treatment of hypertension. The major limitations are as follows: the drug is ordinarily not a highly potent hypotensive agent; and its use is attended with a number of unpleasant side effects, the most serious being an occasional severe depressive reaction[9-12] or stimulation of peptic-ulcer activity.[13] Because of these limitations we thought it worth while to determine by clinical trial whether or not *R. canescens* possesses any advantages over *R. serpentina* in the treatment of essential hypertension.§

Procedure

Selection of Patients

Nineteen patients were selected from those who had participated in a previous study in which *R. serpentina* (whole root) was compared with reserpine in the treatment of hypertension.[10] All were ambulatory patients whose average blood pressure exceeded 165 systolic, 90 diastolic, during an observation period of three or more months before the study. Each patient had ample clinical records verifying

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§All medicines and placebos used in this study kindly supplied by E. R. Squibb and Sons, New York City.

the presence of chronic and sustained hypertension that was not secondary to any known cause.

Composition of Sample

Of the 19 white adult patients selected, 6 were men and 13 were women. Their ages ranged from forty-one to seventy-one years, with an average of fifty-six years. The duration of hypertension since its discovery varied from two to twenty-seven years, with an average of thirteen years. The average blood pressure for all patients before the study was 196 systolic, 113 diastolic.

Examination of the ocular fundi revealed 18 persons with hypertensive changes of Group 1 or 2 according to the Keith–Wagener–Barker classification. One patient had retinal findings classed as Group 3. The concentration of blood urea was within normal limits in all but 2 patients, and the values for these 2 were 46 and 76 mg. per 100 ml. Two persons had residual evidence of previous cerebral infarction, and 3 others had complaints that were quite probably related to cerebrovascular disease. A number of patients had some cardiac abnormality, as follows: 10 patients had changes in the electrocardiograms suggestive of hypertrophy of the left ventricle; 8 showed definite enlargement of the cardiac silhouette on routine roentgenographic examination of the thorax; and 4 gave a history compatible with insufficiency of the coronary arteries, 1 of these having sustained a previous myocardial infarction.

TABLE 1. *Combined Average Values for Blood Pressure and Pulse Rate for All Patients during Various Periods of the Study.*

DETERMINATION	TREATMENT PERIOD			
	BEFORE STUDY	*R. serpentina*	PLACEBO*	*R. canescens*
Systolic pressure	196	168	185	163
Diastolic pressure	113	98	110	98
Pulse rate	80	66	79	68

*Values observed during 3d month of administration.

Methods

All patients underwent complete physical and laboratory examinations before the study was begun. Thereafter, each patient came in weekly at his convenience, and after a period of rest, the blood pressure was taken several times by a physician while the patient was in a sitting position. The two lowest readings together with the pulse rate were recorded, along with relevant notes about the patient's progress and about side effects. Any additional examination that was needed could be carried out at these visits.

A placebo was given for three months, followed by administration of the active drug, *R. canescens* (whole root), in the amount of two 100-mg. tablets taken twice daily for two months. All tablets, placebo or active drug, appeared identical and were given in the same manner, the nature of their contents being unknown to either patients or examiners. A second phase of this study concerned the continued use of *R. canescens* in treatment over an additional period of six to eight months. During this time the effects of change in the amount and frequency of administration of the drug were observed. At the conclusion of the study, a year after its beginning, all patients were again examined completely.

RESULTS

The 19 patients were exceptionally co-operative, and all completed the year's period of study without major difficulty. Immediately before this investigation the same patients had participated in a controlled study during which the whole root of *R. serpentina* had been given in the amount of 400 mg. daily for two months. The results of the previous study could be compared with those of the present study, in which *R. canescens* was administered in similar dosage for the same length of time and under similar circumstances.

Since the effects of Rauwolfia are known to last as long as two months after administration has been stopped, the placebo was given for three months before the use of *R. canescens* was begun. We found that the combined average values for blood pressure for all patients during the second month of placebo administration was 176 systolic, 106 diastolic, as contrasted with 185 systolic, 110 diastolic, for the third month on placebo. The latter figures more accurately portray an untreated control observation even though the values were distinctly less than those found before any Rauwolfia preparations were used (Table 1).

Effect on Blood Pressure

A comparison of the combined average values for blood pressure during the various periods of observation is presented in Table 1. Although average diastolic pressures were the same for both drugs, *R. canescens* produced an average reduction in systolic pressure that was 5 mm. greater than that produced by *R. serpentina*. From Table 2 it can be noted that *R. canescens* was somewhat more effective in reducing diastolic pressure to lower ranges. Both drugs reduced the average diastolic pressure by 15 mm. of mercury or more from placebo values in 7 patients (37 per cent). *R. canescens* reduced the average systolic pressure by 25 mm. or more from placebo values in 7 patients (37 per cent), and a similar result was observed in only 5 patients (26 per cent) treated with *R. serpentina*. Nearly all patients who responded satisfactorily to one drug also obtained good results with the other drug.

Effect on Pulse

The ability of both drugs to slow the pulse rate

was evident in nearly every patient regardless of the effect on blood pressure (Table 2). A decrease in pulse rate almost always occurred sooner than any appreciable decrease in blood pressure, and in a similar manner the pulse rate returned more promptly than the blood pressure to pretreatment levels after use of the drugs had been stopped. It appeared that *R. serpentina* was slightly more effective than *R. canescens* in slowing the pulse rate. Wilson and Wimberley[14] have reported that *R. serpentina* (whole root) apparently produces premature ventricular contractions in some patients, but this was not observed in the patients comprising the present study.

TABLE 2. *Average Range of Blood Pressure and Pulse Rate before and during Treatment.*

DETERMINATION	BEFORE STUDY		ON *R. serpentina*		ON *R. canescens*		ON PLACEBO	
	NO. OF PATIENTS	PERCENTAGE	NO. OF PATIENTS	PERCENTAGE	NO. OF PATIENTS	PERCENTAGE	NO. OF PATIENTS	PERCENTAGE
Systolic pressure:								
140-159	—	—	7	37	10	53	2	11
160-179	4	21	8	42	6	32	7	37
180-199	7	37	2	11	2	11	7	37
200-219	6	32	1	5	1	5	1	5
220-250	2	11	1	5	—	—	2	11
Diastolic pressure:								
75-89	—	—	7	37	5	26	—	—
90-104	4	21	7	37	11	58	6	32
105-119	10	53	4	21	2	11	9	47
120-134	4	21	—	—	1	5	3	16
135+	1	5	1	5	—	—	1	5
Pulse rate:								
50-59	—	—	4	21	2	11	—	—
60-69	3	16	10	53	10	53	4	21
70-79	6	32	4	21	5	26	7	37
80-89	6	32	1	5	2	11	5	26
90+	4	21	—	—	—	—	3	16

Side Effects

The side effects of the two drugs are compared in Table 3. The drugs had similar types of side effects, and their order of prevalence was roughly the same. Of the total complaints, 65 occurred during the use of *R. serpentina*, 42 during the use of *R. canescens*, and only 14 during the use of the placebo. Thus, it seems that the use of *R. canescens* was associated with fewer side effects, and in general these were not as severe as those encountered in the use of *R. serpentina*. However, the interpretation of subjective symptoms was always most difficult, and it is possible that by the time *R. canescens* was used the patients were more accustomed to the various side effects. Thus, they might not have complained as noticeably later as during the initial period when *R. serpentina* was administered.

Increased appetite was noted by nearly every patient during the administration of either drug, with a resulting average gain of 1.4 kg. (3.3 pounds) per person while they were taking *R. serpentina* and a gain of 1.5 kg. (3.4 pounds) per person while they were taking *R. canescens*. Nasal congestion, especially when the patients were supine, was most annoying but did not force any patient to discontinue the study. Perhaps the most pronounced difference between the two drugs from the standpoint of side effects was in the degree of sedative effect experienced. Thirteen patients believed that the sedation experienced with the use of *R. serpentina* was excessive, and only 6 patients thought that this was so during the administration of *R. canescens*. One patient experienced a mild depressive episode while taking *R. canescens* but recovered without altering the dosage. Gastrointestinal effects other than increased appetite were manifested chiefly by increased abdominal cramping and diarrhea. No peptic-ulcer activity was observed in any patient even though Rauwolfia is known to stimulate gastric secretion.[15]

Results of Prolonged Treatment and Change in Dosage

All patients continued treatment with 400 mg. of *R. canescens* a day for nearly five months. As shown in Table 4, this additional period of treatment resulted in very little further reduction of the average blood pressure, so that a maximal effect was almost always present after two months of therapy. At this point in the study, the 12 patients who had obtained a significant reduction in blood pressure were given half their previous daily dose (200 mg. instead of 400 mg.), which was taken once a day instead of twice.

The remaining 7 patients, whose blood pressure was not substantially reduced by the original dose, were given 300 mg. twice daily, making an increase of 50 per cent in dose. From Table 4 it is apparent that very little change in blood pressure or pulse rate occurred as a result of these changes in dose. Patients whose blood pressure was responsive initially to therapy with *R. canescens* remained responsive on the lesser dose given once daily, and blood pressures refractory to treatment at first remained refractory in spite of increased dosage.

The reduction in dose also resulted in amelioration of the severity of side effects experienced by susceptible persons taking the original dose. The opposite was true regarding the 7 patients taking an increased dose of the drug, since 4 of them experienced an undesirable increase in side effects. It was interesting that after four months of taking the increased dose, 2 patients experienced a depressive reaction of mild to moderate severity. No similar reaction had been observed previously in these 2 patients although they had been followed at the Clinic for many years. In 1 case use of the drug was discontinued, and in the other the dose was decreased by two thirds. Both patients were followed closely, and both had definite lessening of the depression during the ensuing three months.

TABLE 3. *Comparison of Side Effects Occurring during Treatment.*

SIDE EFFECT	*R. serpentina*		*R. canescens*	
	NO. OF PATIENTS	PERCENTAGE	NO. OF PATIENTS	PERCENTAGE
Gain of weight	18	95	13	68
Nasal congestion	15	79	13	68
Excessive sedation	13	68	6	32
Dreaming or nightmares	9	47	6	32
Laxative effect	4	21	2	11
Depression	—	—	1	5
Miscellaneous complaints	6	32	1	5

At the conclusion of the study, a year after its start, nearly every patient wished to continue taking the drug and thought that he had received benefit from it. This improvement was related to a feeling of well-being and a lack of former tenseness that more than made up for the frequent, annoying side effects.

Upon re-examination of the ocular fundi 6 patients showed improvement in the hypertensive changes, 2 showed slight worsening, and the remaining 11 showed no change. At this time the values for blood urea in the 2 persons with originally elevated levels had decreased from 46 and 76 mg. to 34 and 56 mg. per 100 ml. respectively. Two additional patients who had normal values for blood urea at the beginning now had values of 42 mg. per 100 ml. Patients with complaints referable to cerebrovascular disease showed no objective change in their status at the end of the study. Of the 4 patients with pain from insufficiency of the coronary arteries, 3 seemed improved in this regard at the time of re-evaluation. Three of the 10 patients with electrocardiographic evidence of hypertrophy of the left ventricle had tracings that were more nearly normal at the end of the year, whereas the tracings of the remaining 7 were essentially unchanged. Two of the 8 with enlarged cardiac silhouettes in roentgenograms of the thorax at the beginning of the study had normal-sized heart shadows upon its completion.

TABLE 4. *Effect of Prolonged Treatment with* R. canescens *and Change in Dose on Blood Pressure and Pulse Rate.*

GROUP	DOSE OF DRUG*	AVERAGE DURATION OF THERAPY	BLOOD PRESSURE		PULSE RATE
			SYSTOLIC	DIASTOLIC	
	mg. per day	*mo.*			
All patients (19)	400	2.0	163	98	68
		4.8	161	97	67
Responsive patients (12)	400	4.8	149	91	67
	200†	4.3	149	92	69
Refractory patients (7)	400	4.8	178	105	68
	600	3.7	178	103	66

*Divided into 2 doses.
†Given as 1 daily dose.

SUMMARY AND CONCLUSIONS

In this study of 19 patients with mild to moderately severe hypertension there did not appear to be any striking differences between effects of the whole-root preparation of *Rauwolfia canescens* and those of a similar preparation of *R. serpentina*. This similarity of results pertained not only to effects on blood pressure and pulse rate but also to side effects. If any difference existed, it was that *R. canescens* tended to have fewer and less severe side effects. In particular, it seemed to have less sedative effect than *R. serpentina*. Depressive reactions that have been observed among hypertensive persons treated with preparations of *R. serpentina* are also associated with the use of *R. canescens*.

Continued use of *R. canescens* was well tolerated over a period of eight or nine months, and only when the dosage was increased did more troublesome side effects develop. In patients who initially obtained a satisfactory reduction of blood pressure — about 40 per cent of those treated — it was possible to maintain this improvement even though the dose was cut by half and given once daily instead of twice. In this group there was no evidence of the development of "resistance" to the drug. Patients whose blood pressure was not lowered appreciably by the use of *R. canescens* in moderate doses did not respond sig-

nificantly when the doses were increased by 50 per cent. This suggests that if there has not been a satisfactory reduction in blood pressure after two months of treatment with moderate doses of *R. canescens*, it is unlikely that an increase in the dose will result in further benefit. On the other hand, if a good reduction of blood pressure has been obtained, it seems reasonable to expect that decreased dosage of the drug may continue to maintain the good response as well as to lessen the frequency and severity of side effects.

R. canescens is considered to be a potent pharmacologic agent whose use should be carefully supervised.

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SPECIAL ARTICLE

MEDICAL EDUCATION TOMORROW*

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WHEN this association was founded in 1886, with the object of advancing scientific and practical medicine, there was very little that could be called scientific medicine as it is known today. Practical medicine was based largely upon tradition, magic and empiricism. Medical education was carried out for the most part in schools where the preceptorship and the lecture were emphasized, and university medical education was largely undeveloped or nonexistent.

About the time of the first meeting, however, a new ferment was working, and a revolution was being introduced into all science, especially the biologic sciences. This revolution has proved to be the foundation of the scientific medicine of the present time.

The growth and development of the biologic sciences, beginning in the nineteenth century, have had their most profound influence on medicine and its practice during the first half of this century. The deep influence of science is now being felt in medical practice on a large scale, in full tide of the accomplishments that started seventy-five years ago. This progress will continue, provided the problems that lie ahead are viewed in biologic perspective, and that the basic sciences and medical education are given the support they deserve and need for their full growth and development.

This association, through its membership, has promoted and encouraged advances in medicine by emphasizing the extension of research in the basic and clinical sciences, and by improving and extending medical education with university ideals. Since this is the keystone of the arch for meeting the objective, the benefits that have flowed to mankind have shown themselves in an increase in both the quality and the quantity of available medical care. This progressive improvement in medical care or in practical medicine has been due to the expansion and improvement of medical education integrally related to research. This is my first point. It is one that must be placed before the public, the profession and the lawmakers who are vitally concerned with improving the health and medical care of the people. It is a point to be underscored again and again.

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When any group becomes completely absorbed in an enterprise or an idea, it is a good thing to stand off from it now and again, and look at the picture from the most dispassionate point of view possible. Medical education and research are no exceptions. Quite rightly, all major efforts must today be devoted to the urgent business of making sure that the best job possible is being done and that the future is being planned for. It not only will do no harm but also will actually be of service, if now and again physicians try to get outside the immediate problem and to look at it as objectively as they can, in long perspective.

It has been said that the biologist has the longest possible perspective. Now, when medical education is pinned out as in the biologist's collection, what does it look like? What should be added, and what should be discarded? In any plan for improving the medical education of the future, it is necessary to examine the past as well as the present and to develop foresight. People must be emotionally prepared to live within the framework that the medical profession is helping to create.

Many surveys of medical education, medical research and health have been made during the past fifty years, which have witnessed many improvements, great changes and great growth. From a study of these surveys and from an examination of the facts, it is apparent that within the past fifty years able men with a scientific outlook have been fed into medicine. A rapid transformation of medicine from a magical art into a scientific discipline has taken place, with dependence less upon tradition and empiricism and more upon science. Medical practice has changed so that there is greater emphasis on problems of health supervision and maintenance, and the prevention of illness. Great strides have been made in the cure or healing of some illnesses, in prolonging life and in reducing the degree of physical disability and impairment. The sum of this is very great indeed. The basic reason for all these improvements and changes is the advancement of science and technology, and the improvement and extension of medical education stemming from the universities.

This association, as an organized body, has studiously avoided discussion of the socioeconomic aspects of medicine, because the more medicine rests on these bases, the more political it becomes, with its nonprofessional control of standards and technics. But, because advancing scientific and practical medicine is concerned with economics, and research and education have become problems of cost, the medical scientists, like all scientists, have been forced to look more and more to the state for support of their work — just as the public has looked to the state for more and more tax support of medical care. This brings the practicing physician and the medical scientists face to face with the problems of planning and of control of research and education. It brings them face to face with the problem of governmental control versus private control. These problems call for *individual* participation in affairs of the community and government, and in the future, more and more physicians and more and more scientists are going to be asked for impartial advice about health and education. All physicians, as individual citizens, must be prepared to provide this advice, based upon careful and dispassionate examination of the problems, and experimentation, flexibility and freedom of action must be encouraged.

Public Reaction to Medical Advances

As members of the dedicated profession of scientists physicians should examine some of the public reactions to the advances in medical science and practice, because these advances have created certain social and economic changes in our society. The public looks to the scientist and to the physician for future guidance so far as all matters of health are concerned. There is a heightened interest on the part of the public in all health problems. There is a renewed public confidence in the profession, which has come into a position of greater respect and inevitable leadership. The word of the medical scientist and the physician carries new weight and authority. Their judgments have an impact that extends far beyond the profession. There is a new public interest in all science, and this has been intensified by the development of atomic energy and the discovery and application of a wide variety of useful products such as antiinfective agents, steroid hormones, vitamin B_{12} and many others. All people want to know how these scientific advances will help them personally, because the one obvious fact that is appreciated by the public is the practical application of the basic sciences to their well-being and happiness. It is something that everyone can see and feel.

The progress of medical science has affected health and life expectancy. The development of new drugs and new technics for diagnosis and treatment, the promotion of health, the prevention of illness, the rehabilitation of the sick and injured and their restoration to useful living has created an increasing public awareness of the importance of health and of the war that is being waged against disease and impairments. The public is conscious of the concentrated attacks that are being made upon disease, and is being urged to support research, education and practical medicine on a scale that was undreamed of twenty-five years ago.

The dimes and dollars roll and march; the taxes and the federal and state appropriations for health increase, and there are continuing crusades against heart disease, cancer, arthritis and rheumatism, mental illness, poliomyelitis, multiple sclerosis and a host of other diseases that are unsolved problems today. When the scientist comes out of his laboratory accom-

panied by professional public-relations counselors carrying fat briefcases filled with handouts, and makes an appearance and a pronouncement, he steps into the spotlight and becomes a public figure. The impact of these dramatic pronouncements on the public is far reaching, and their implications become the concern of government and private industry. They call for federal and state subsidy as well as congressional inquiry and investigation. They affect the organization, the planning and the financing of scientific research, and they create a searching inquiry for a better and more popular understanding of what a medical scientist does and how the fruits of his work benefit mankind. Public announcements regarding a possible cause of cancer of the lung or of heart disease can shake a large and prosperous American industry. A secret serum alleged to have an effect on cancer can upset a university, convulse a community, unsettle the politics of a legislature and have far-reaching effects on the search for the truth about cancer.

The announcement of the development of a vaccine against poliomyelitis can rock the nation, call for congressional investigations and stimulate demands for centralized governmental control of all aspects of vaccine production, including its manufacture, cost, distribution, purchase and use.

The scientist today is becoming more and more dependent upon the public for support. The public in turn is being urged and pressed to support scientific research and education, either through voluntary contributions or through taxation. Thus, the medical scientist today is face to face with a public that has been aroused about health and about the importance of research. It is also aroused about medical practice and care, and especially about its high costs. *But the public is not sufficiently well informed about the basic need for the expansion and improvement of medical education integrally related to research.* It must be kept constantly aware that progress and improvement in medical care, both quantitatively and qualitatively, will continue only as medical education is strengthened and extended through its entire range — both undergraduate and graduate — predoctoral and postdoctoral.

My second point, then, is that having aroused the public about health and health improvement, the profession needs to keep its interest high and persuade it that advancement of medicine will continue in the future only if medical schools continue to be strengthened and excellent doctors continue to be trained for the future.

In the past the leaders in American medicine have been concerned with advancing their profession, and I have stated that this has been achieved through improvement in medical education with university ideals. It is well to re-examine the aims and objectives of medical education. I submit that the aims of university medical education today and in the future will be basically unchanged, although the means of achieving the objectives will change. The function of the physician and his relation to society will shift, and he needs to be prepared to face and meet the changes that he has helped to create. The public needs to be kept well informed that these changes are for its benefit.

Aims of the University in Medical Education

It has been the basic aim of every university worthy of the name to advance, preserve and transmit knowledge in all the basic and applied medical sciences over the entire range of its activities. In this way, young people are educated and prepared for professional service to society and for well adjusted personal lives in their professions. The universities have the responsibility for educating a new generation of doctors and medical scientists. There is no controversy over the basic aims of a university regarding medical education, but the ways of meeting the objectives have varied from time to time and are under constant examination and re-examination.

When I refer to university medical education, I mean undergraduate medical education — that is, educating the youth who are qualifying for the degree of "doctor of medicine." This is the prime objective of medical schools and should receive the first and highest priority. This indispensable service to the community and to society is basic to all discussions of medical education. The development of strong programs for graduate training in the clinical sciences with intern, residency, fellowship and training programs takes a secondary place with the university except as these activities support and strengthen in a most important way undergraduate teaching and medical research.

Function of the Physician

Before the ways in which the universities may educate the practitioner of the future are discussed, his functions should be discussed, and the way in which he needs to be educated to meet the problems that lie ahead considered. Every generation has its ideal doctor. The ideal doctor of today will differ from the ideal doctor of tomorrow. He has always been shaped by the society in which he lives, and his function changes with the times. It has been said that he has always been a subtle blend of the social, economic and technical forces existent at the time. He has been the product of his education and training, and his practice is often modified to fit the mores of his community. With advances in medical education it is well to develop some foresight into the future role of the physician in society and attempt to make a blueprint of what is to come.

The new physician should be adequately trained in science, but he should be more than a scientific specialist, skilled in his specific branch of work. He must be an educated person who is welcome in society for

his own sake, and he must remain in close touch with the people he serves. His object will be to direct his efforts toward the prevention of illness and the healing and rehabilitation of the sick by weaving science and humanism into one fabric. This combination in a single picture sets the goal that the new physician must strive to reach. Since too little is known about preventive medicine, and since it frequently breaks down or fails, the doctor will continue to be the therapist, or the member of a team of therapists.

The public is interested in a healthy and happy life. The late Henry L. Mencken said that it was a doctor's function to make it possible for his patients to go on doing the pleasant things that are bad for them — smoking too much, eating too much, drinking too much and the rest of them — without killing themselves any sooner than is necessary. To fulfill such a function will require more knowledge concerning health as well as disease.

Specialization in all the sciences will increase, and research will be promoted by all means available. There will be a need for more specialists in psychiatry and in the social sciences, and these specialists will need to intensify sociologic research, which aims at studying the life cycle of man in his social environment.

I should like to end this section on the function of the practitioner by saying that if he is to apply his knowledge and his training in the most effective way for the benefit of people, he must have access to facilities that will enable him to do so. This is a local community problem. Moreover, society in general, or the physician's public, must be educated by example and by demonstration to realize that the practices that he advocates are in keeping with his mission in life — that is, to promote and preserve health and to provide the best medical care that is possible for the well-being of his patients. Society will dictate the kind of practitioner it will train, and it will dictate the kind of medical care it will accept and pay for. When people are convinced that they are receiving the full benefits of improved medical education, they will be willing to support it. "With the support of the people, anything is possible — without it, nothing is possible." It was Virchow who learned, much to his disappointment, in his crusade for medical reform that his program failed because it was designed for the people but without them.

In short, as I see it, the function of the physician in the future will be to advance medicine and to provide for society professional service of high quality. He should be educated so that he is capable of becoming a leader and a friend in his local community for the promotion of health. He must be more than a person who is concerned only with the care of the sick and injured, but rather a person who looks at and studies health as well as disease — one who aids in maintaining and supervising health, a person who advises and educates the public by providing the best health and medical care that is accessible. To accomplish this will require some reorganization directed toward encouraging society to provide for continued pursuit of the educational ideals of the modern university. It will require the proper emphasis upon the study of the patient so that the patient will not say, "I wish the doctor would look at me more and at the x-rays less." It will require well prepared students, adequate facilities, sufficient financial support and a staff of highly qualified scientists and clinicians who are dedicated to educating the doctors of tomorrow.

Preparation of the Future Physician

The student should be brought under the intellectual influence of a band of imaginative scholars who treat learning in an imaginative way. The physician of the future needs to be educated in a manner that will arouse his intellectual curiosity and preserve his imagination, because youth is imaginative. This imagination must be strengthened by discipline because, as Whitehead has said, when the imagination of youth is welded with the experience of the teacher, it can be preserved throughout life.

The university medical school should provide its students with the greatest opportunity for self-development with the particular medical career in view in which they will be active in the years ahead. If one fails to provide a student with this opportunity during the best period in life and insists upon rigid conformity in training and curriculum, and overemphasis on technical training, one is apt to damage the energies of the mind that should direct this acquired technical skill. Prolonged routine work dulls the imagination and may stunt the promise of youth for years. Technical skill and excellence, usually acquired by the doctor after graduation, need to be guided by lifelong imagination. The student who passes into his hospital training or the period of intensive technical apprenticeship should have his imagination fired by connecting the essential details he has acquired in the medical school with the general principles underlying a career in medicine. The student must learn early in his education that he is being prepared for an intellectual career, and a university should promote the general principles underlying such a career. In this way, the youth can be educated and prepared for his profession.

Now, I believe that there are two basic ingredients necessary for a university medical school to meet its aims and objectives — its faculty and its students — because the combined efforts of the teacher and the students create the product. When students are well prepared in the basic sciences, when they are able, industrious, intelligent and responsive and free to engage in intellectual and cultural pursuits and when opportunities are extended to them by teachers who are masters of their subjects and gifted with the

power of arousing interest in them, the results of medical education will reach their full potential. President Lowell once said in his essay on "Tools and the Man," "After all, the most important thing is not what is taught but what is learned, not what goeth into the belly but what cometh out of the heart, or in the language of modern psychology, not what goes into the ear but what comes out of the brain."

Medical education in the United States began to flourish when society, mainly through private philanthropy functioning through the foundations, provided capital funds for establishing and improving medical schools upon the university pattern. These capital funds were used for the support of the faculty. Today, medical education is more and more dependent upon society for support through tax funds and from a broad personal base of contributions, mainly for short-term projects of research and education. There is a need to reverse the trend so that the universities have greater sustained financial support. Many medical schools are becoming what Jonathan Swift called in *Gulliver's Travels,* "Academies of Projectors" — where the projectors came up with innumerable happy proposals and were driven on equally by hope and despair.

Certainly, if the universities are going to meet their responsibilities to society in the field of medical education, they will need more dependable income for the employment of excellent teachers who are primarily interested in advancing knowledge and transmitting it to youth. The university medical schools urgently need to improve their facilities and their faculties for the education of their students, and the students need greater support if they are to be freed from much outside work so that they can devote their full time to self-development for the career of medicine.

To meet these needs requires foresight, flexibility in program and romance — a willingness and freedom to experiment and take a few adventures into the unknown. It requires freedom from rigid conformity, and freedom from calcification of the categories. It requires a vigorous campaign of public education about the financial as well as the objective needs of university medical schools. The universities must take the leadership and focus attention on their current and future problems. University medical schools need to inform the public that they are pursuing ideals that are necessary to provide the best practitioners of the future — doctors who are interested in giving the best medical care available. The public will be willing to provide ample support for the education and training of physicians so long as they have confidence that they are being trained to render to society professional service of high quality.

The universities should undertake research in the learning process, and explore the best methods of stimulating, guiding, promoting and improving the methods for the self-development of medical students. They need to keep the spirit of intellectual adventure and the joy of discovery alive. They need to pioneer in developing new technics and in leading the way to a more fruitful school experience. I repeat that the most valuable intellectual development for the doctor of the future is self-development, and its greatest period is between the ages of sixteen and thirty years — the time when most students are preparing for their mission in life — their college years, their medical-school years and their hospital-training years. This period needs to be examined as a whole, and programs of flexibility developed to improve these opportunities. Again, in the words of Whitehead:

> The students are alive and the purpose of education is to stimulate and guide their self-development. It follows as a corollary from this premise that the teachers also should be alive with living thoughts.

Physicians must create a common cause with society in an effort to build a finer profession.

Conclusions

I shall conclude by saying that the responsibilities of the members of this association for advancing scientific and practical medicine in the future are very great indeed. As individual members of the profession their actions and leadership will shape and determine the destiny of medical education and hence the medical practice of the future. Since nothing worth while is accomplished without human resources, it follows that one must find the men who know the trends — the future needs — and, what is more important, men who understand that the future of medicine and the future quality and quantity of medical care rest firmly on the rock of excellent medical education, not just good medical education.

In this period of transition between private and public support of medical education and research, one must destroy the barriers between medical schools and the public inherited from the past in the sheltered period of relative independence and freedom from community support. The public must be taught by example and by indoctrination that the emphasis must be placed on university medicine and that through its extension and improvement, the social and economic problems with which they are concerned and that are intimately related to medical care can be solved. To fulfill these goals and to advance their objectives, the universities need greater financial support and greater public understanding. They need more dependable and more unrestricted income for the support of their faculties; they need more support for the training of the medical teachers of the future; they need more support for talented students, and a more balanced support for postgraduate education and training. This support can be obtained if they can convince the public that the

medical schools are pursuing a course designed to benefit and help it. The universities must build into society the demand for the ideal physician of tomorrow that they seek to train.

In all these efforts, one must not confuse basic medical education with technical training. One must distinguish between the two and weave them into the same fabric. Thought must be given to the future because the profession is primarily concerned with educating a new generation. Physicians should not be men who practice the errors of their ancestors — Disraeli's definition of practical men — and should not believe that progress consists only in discarding the things of the past.

MEDICAL PROGRESS

APPLICATION OF HOMEOSTATIC PRINCIPLES TO THE MANAGEMENT OF NEPHRITIC PATIENTS*

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THE neuroendocrine-renal homeostatic mechanisms keep the water and electrolyte content of the body within physiologic limits by adjusting the urinary output of water and solutes in accordance with homeostatic needs. The functional capacity of these mechanisms normally is so large that healthy persons can vary their intake of foodstuffs and fluids over a wide range without suffering grossly perceptible metabolic disturbances. By contrast, the homeostatic capacity of patients with marked impairment of renal function may become so reduced that the intake of food and fluids must be kept within certain relatively narrow limits if water and solute intoxication and depletion are to be avoided.

The present communication considers the possibility that the management of patients with severe limitation in renal function is facilitated by obtaining quantitative information concerning the clinically significant limitations in homeostatic function suffered by each individual patient, making water and other nutrients available to the patient at rates that fall within the residual "safe working ranges" defined by his specific limitations and employing therapeutic regimens that, while falling within the limits mentioned above, will tend if anything to augment these ranges.

These considerations will be introduced in the section that follows by an abbreviated review of available information concerning normal bodily limits of tolerance for water and certain important dietary constituents and their relation to ordinary dietary intake.

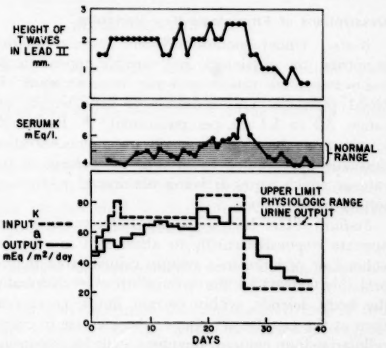

FIGURE 1. *Demonstration of the Physiologic Maximum Tolerance Level for Potassium (That Is, the Potassium Ceiling) in a Patient with Impaired Kidneys.*

NORMAL RELATIONS BETWEEN PHYSIOLOGIC MINIMUM REQUIREMENTS, PHYSIOLOGIC MAXIMUM TOLERANCES AND ORDINARY DIETARY INTAKE

Because the kidneys constitute the chief route by which the majority of dietary solutes are excreted in a facultatively controlled manner,[1,2] their limits of capacity to conserve and to eliminate in accordance with homeostatic needs may be considered basic determinants of safe ranges of intake. Renal capacity to accomplish these tasks is bounded on the one hand

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by *physiologic minimum output or "floor" values* and on the other by *physiologic maximum* output or "ceiling" values.[3,4]

Rates of output outside these limits may occur, but only at the expense of a pathologic deviation in the physiologic key variable. It follows that rates of urinary output of a substance found at times when the key variable is abnormally low lie below the floor level. Similarly, rates of urinary output found at times when the corresponding key variable is abnormally high lie above the physiologic ceiling level. This phenomenon will be exemplified below in connection with Figure 1.

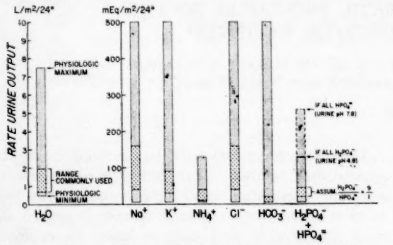

FIGURE 2. *Approximate Physiologic Maximum and Minimum Rates of Urinary Output.*

Descriptions of Physiologic Key Variables

Water. Under conditions where vascular volume is normal, the physiologic key variable appears to be the water-solute ratio (or water concentration) in blood plasma.[5] This normally is kept within the range, 3.5 to 3.7 ml. per milliosmol.[6,7]* Pathologic lowering or elevation of serum water concentration normally is prevented by suitable adjustment of the rate at which water is being eliminated relative to solutes in the urine.

Sodium. The body's sodium homeostatic system appears responsive chiefly to alterations in vascular volume or pressure in a certain critical area that is probably located in the arterial tree.[9,10] Normally, the body defends, within certain limits, concentrations at the expense of volume. An increase in extracellular sodium content, therefore, calls for expansion of extracellular volume in the ratio of about 3.6 ml. per milliosmol of sodium (see preceding section) plus 3.6 ml. per milliosmol of the companion anions (that is, chloride, bicarbonate and so forth) that necessarily accompany fixed base in extracellular fluid. The reverse normally occurs when extracellular sodium content decreases.† Accordingly, one may judge body sodium status indirectly by noting whether the patient shows clinical evidences of extracellular dehydration (too little sodium), normal hydration (correct amount of sodium) or extracellular edema (too much sodium). One would expect the person with too little sodium to have reduced urinary sodium output to the lowest rate of which he is capable. Likewise, the person with too much sodium should be excreting sodium at the greatest rate of which he is capable.

When these clinical signs are to be used as indexes of body sodium status, it is necessary to consider the possibility that the sodium-system-sensing element is being influenced by alterations in vascular volume due to factors other than extracellular sodium content. These include, first, primary water overload, which tends to produce hypervolemia, abnormally high serum water concentration (often with hyponatremia) and sodium diuresis[13] and, secondly, conditions like hypoalbuminemia, hepatic cirrhosis and cardiac failure that tend, probably by causing a lowering in arterial volume or pressure, or both, to prompt increased aldosterone production, sodium retention and edema formation.[10,14]

TABLE 1. *Extrarenal Losses Assumed in the Calculation of Oral Requirements and Tolerances.*

METHOD OF EXCRETION	RATE OF LOSS					
	WATER	SODIUM	POTASSIUM	CHLORIDE	PHOSPHORUS	NITROGEN
	ml./sq.m./day	*milli-mols/sq.m./day*	*milli-mols/sq.m./day*	*milli-mols/sq.m./day*	*milli-mols/sq.m./day*	*gm./sq.m./day*
Stool	60	3	7	2	10	1
Lungs & skin	1200*	<1	<1	<1	<1	<1
	700†					

*Infants.
†Adults.

Potassium. Little is known concerning the exact location and nature of the body's potassium-homeostasis-sensing element. Despite this it seems reasonably clear that the body normally attempts to excrete potassium at maximal rates under conditions of hyperkalemia or cellular potassium excess, or both, which may be reflected in electrocardiograms by peaking of the T waves,[4,15] Contrariwise, there is a tendency to conserve potassium maximally under conditions of simple cellular potassium deficit.[12] Unfortunately, it is difficult to recognize the latter state other than by means of isotope-tracer measurements or detailed metabolic-balance studies. It appears that the two most commonly mentioned signs of cellular potassium lack — namely, hypokalemia in association with hypochloremic alkalosis and flattening of the electrocardiographic T waves — may in actuality reflect the occurrence of cellular sodium plus hydrogen ion intoxication in persons suffering cellular potassium deficiency.[16]‡ In contrast to patients with

*The body's neurohypophyseal serum water-concentration homeostatic sensing element appears to be influenced also by changes in hydrostatic pressure in its immediate environment, decreases and increases in pressure, respectively, tending to have the same type of effect as decreases and increases in the water-solute ratio of the serum.[8]

†Under conditions of cellular potassium depletion, excessive amounts of sodium may be stored within body cells. Under this circumstance, metabolic alkalosis may be the most readily available indicator of excess body sodium storage.[11,12]

‡Cellular potassium may be replaced by sodium plus hydrogen ion at a ratio of approximately two sodium plus one hydrogen for each three potassium ions.[16]

simple cellular potassium lack, those with the syndrome of cellular sodium plus hydrogen ion intoxication and potassium ion insufficiency may fail to conserve potassium with maximal efficiency at the kidney.[12] Renal excretion of potassium also may continue at supraminimal rates even though body potassium stores are depleted under conditions where the ammonium ion and other fixed-base conserving mechanisms are overburdened or defective.

Chloride and ammonium ion. For chloride, the physiologic key variables appear to be body fluid pH and serum chloride concentration. There is a strong tendency to chloride conservation under conditions of simple extracellular hypochloremic alkalosis.[1] This tendency may be negated by the occurrence of intracellular acidosis of the type mentioned above when sodium and hydrogen ions enter the potassium-depleted cell. Here, in the presence of extracellular hypochloremic alkalosis, the urine is apt to be of acid reaction and of considerable chloride content.[12] Conversely, there is a strong tendency to chloride elimination under conditions of extracellular hyperchloremic acidosis.[1]

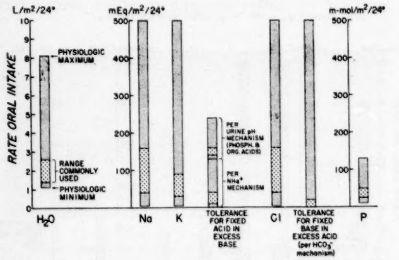

FIGURE 3. *Approximate Maximum and Minimum Limits to Physiologically Tolerable Rates of Oral Intake.*

Urinary ammonium ion excretion is stimulated under conditions where there is need to conserve body stores of fixed base in the presence of obligatory anion excretion.[17,18] Strong stimulus to ammonium ion secretion ordinarily exists in patients suffering acidosis due to accumulation of chloride, sulfate, nitrate or ketoacid ions or to primary alkali loss.[12,19]

Bicarbonate. Rise in serum pH by loading with fixed base as in gastric vomiting appears the key variable to increase in urine pH and bicarbonate excretion.[1]

Phosphorus. The chief normal stimuli to maximal phosphorus elimination by the kidneys are simple hyperphosphatemia and hypocalcemia. Both stimuli induce phosphaturia by prompting increased parathyroid activity.[5] Urinary phosphorus output normally falls to minimal levels under conditions where tendencies to hyperphosphatemia and to hypocalcemia are absent.[5]

Time Required for Adaptation to Changes in Rate of Intake

In relating rates of urinary excretion of water and various solutes to bodily status, attention must be paid to the fact that the body requires time to adjust urinary outgo in accordance with homeostatic needs after an abrupt change in rate of intake.

The longest intervals that normally may be required to attain full adjustment of urinary output after the development of maximum need are approximately as follows: water, two hours; sodium, potassium, ammonium and chloride, five to seven

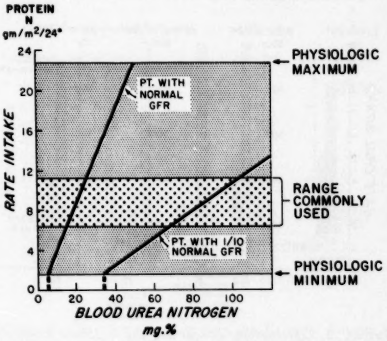

FIGURE 4. *Approximate Relations between Protein Intake and Blood Urea Nitrogen Concentration in Persons with a Normal Glomerular Filtration Rate (GFR) and in a Subject Whose Rate Has Become Reduced to One Tenth the Normal Value.*

days; bicarbonate, less than one day; phosphorus, one or two days.[1,5,7,12,20-27] These time requirements may be shortened if the patient has made similar adjustments in the recent past.

Procedure for Determination of Physiologic Maximum and Minimum Rates of Urinary Excretion

One can determine that an observed rate of urinary output is below, within or above physiologic limits by relating it to bodily status as outlined above. To locate the position of a physiologic limit* it may be necessary to carry out a systematic study of relations between intake, output and the physiologic key variable as shown in Figure 1.

The subject of these measurements was a boy with marked impairment of renal function. The measurements were designed to find out whether he could take diets of ordinary potassium content without becoming potassium intoxicated. As shown in the lower section of the figure, his oral intake and urinary output of potassium at the outset of the observations

*For phosphorus, the physiologic maximum values may be calculated with reasonable assurance from the glomerular filtration rate.[21,35] This point is discussed below in connection with Case 1.

were approximately 45 milliequiv. per square meter per day. The upper two sections of the figure show that his serum potassium concentration and electrocardiographic T waves (as measured in Lead 2) were within normal limits at this time. After the initial increase from 50 to 70 milliequiv. per square meter per day, urinary potassium output rose proportionately, and serum potassium concentration and T-wave values were maintained within normal limits. Accordingly, the output rates of 45 to 70 milliequiv. may be said to fall within his safe working range.

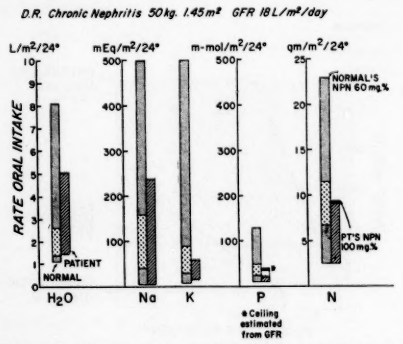

FIGURE 5. *Observations concerning the Residual Ranges of Homeostatic Capacity of D. R., a Twenty-two-Year-Old Man with Chronic Glomerulonephritis (Case 1).*
The weight was 50 kg., the surface area 1.45 sq. meters, and the glomerular filtration rate 18 liters per square meter per twenty-four hours.

When the intake of potassium was further increased from 70 to 85 milliequiv. per square meter per day, urinary potassium excretion increased somewhat, but not in proportion to input. Within a few days serum potassium concentration rose to supranormal levels, and the average amplitude of the T waves increased. Thus, it appeared that the upper limits of this patient's capacity to excrete potassium while maintaining serum potassium concentration within normal limits was approximately 70 milliequiv. per square meter per day. Higher rates of output could be accomplished only at the expense of a pathologic deviation in the physiologic key variable.

Approximate Physiologic Limits of Capacity of Healthy Persons to Vary Rate of Urinary Output of Water and Certain Solutes

For each substance represented in Figure 2, the physiologic maximum or ceiling rate is indicated by the location of the upper end, and the minimum or floor rate is represented by the level of the lower end of the vertical column relative to the ordinate scales. The coarsely speckled section within each column represents in approximate terms the portion of the total range commonly used by healthy persons taking ordinary North American diets.*

The physiologic maximum value for urinary water output is based on data recently obtained by Crawford and his associates.[29] This maximum is somewhat greater than those heretofore indicated for persons with low rates of solute output.[3,5,7]

The physiologic maximum output values for sodium and potassium[20,30] also are higher than those set forth in earlier papers.[3,5] These earlier values were intentionally set at submaximal levels in view of the possibility that patients undergoing parenteral fluid therapy might lack the time necessary to adapt maximally to an abrupt change in rate of input. The body's capacity to eliminate potassium by way of the urine may be reduced below full maximum levels under conditions of sodium depletion.[31] The same limitation may also be true of sodium under conditions of potassium insufficiency.[32]

The ceiling value for ammonium ion has been estimated from observations on persons subjected to ammonium chloride loads or suffering from diabetic ketoacidosis.[1,19,22,24]

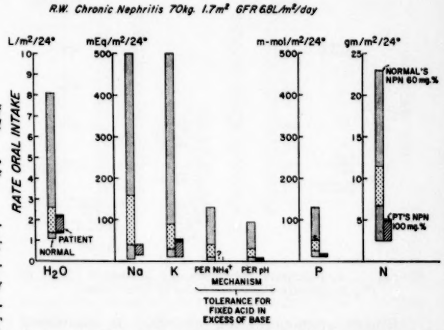

FIGURE 6. *Observations concerning the Residual Ranges of Homeostatic Capacity of R. W., a Twenty-one-Year-Old Patient with Chronic Glomerulonephritis (Case 2).*
The weight was 70 kg., the surface area 1.7 sq. meters, and the glomerular filtration rate 6.8 liters per square meter per twenty-four hours.

Rates of chloride output as high as those indicated here may be observed in persons who are taking large quantities of sodium chloride or potassium chloride.[20,24] The physiologic maximum for this ion, given as an isolated anion in the form of ammonium chloride, may fall to levels similar to that shown for ammonium ion.

For water, sodium and potassium, respectively, the physiologic minimum values are essentially the same as those set forth previously.[3] The corresponding

*These ranges were estimated from average data recorded in the literature[2,19,28] supplemented by information kindly provided by Dr. Jean Mayer, of the Harvard School of Public Health.

values for ammonium, chloride, bicarbonate and phosphate are based on data available in the literature supplemented by measurements carried out in this department.[1,2,5,12,21,30] The floor value for phosphate shown here is lower than that set forth previously.[3] The difference is explained by the fact that the previous estimate of the minimum phosphate needs included not only minimum urine but also an average value for fecal phosphate excretion of 300 mg. (10 millimols) per square meter per day.

Estimation of Ranges of Bodily Tolerance for Water and Certain Substances Taken Orally

These ranges may be found by adding to the urinary values of Figure 2, average minimum normal values for rate of loss by way of the gastrointestinal tract, skin and lungs (Table 1).[2,33] The resultant ranges of tolerance are shown in Figure 3. In the construction of this figure, the total value indicated for "tolerance for fixed acid in excess of base" is shown as the sum of the tolerance provided by the urinary ammonium ion mechanism plus that provided by changing the valence of urinary phosphate and organic acids to minimal values by lowering

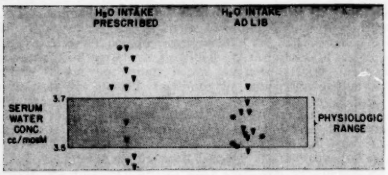

FIGURE 7. *Comparison of Serum Water Concentration in the Patient Shown in Figure 6 (Triangles) When Water Intake Was Prescribed by a Physician (Left) and When It Was Selected by the Patient (Right) — Reproduced from Kerrigan et Al.[3] with the Permission of the Publishers.*

urinary pH to 4.8, the physiologic limit of acidity.[1] Likewise, "tolerance for fixed base in excess of acid" is considered approximately equivalent to the bicarbonate output made possible by maximal alkalinization of the urine to pH 7.8.[1]

These data are supplemented by those of Figure 4, which indicates in approximate terms the relations to be expected between protein intake and blood urea nitrogen concentration in persons with a normal glomerular filtration rate (GFR) and in a patient whose rate has become pathologically reduced to one tenth the normal value.* When Figures 3 and 4 are viewed as a whole, it is interesting to note the generous margins of safety enjoyed by healthy persons taking ordinary diets. The sections that follow will indicate the degree to which these limits of safety may be reduced either directly or indirectly by renal disease.

*In drawing this figure, it has been assumed, as shown in Figure 10, that urea clearance was about 40 per cent of glomerular filtration rate in normal persons whose urine volume of 1 liter is about 1 per cent of glomerular filtrate volume, and about 75 per cent of the rate in the individual whose glomerular filtration rate is 10 per cent of normal and in whom the same urine volume amounts to approximately 10 per cent of the glomerular filtrate volume.

Observations on Certain Direct and Indirect Effects of Renal Disease on Bodily Tolerances for Water and Other Dietary Constituents

The criteria outlined above have been applied to patients with organic renal disease of various degrees of severity. The results obtained on 4 representative patients may be summarized as follows:

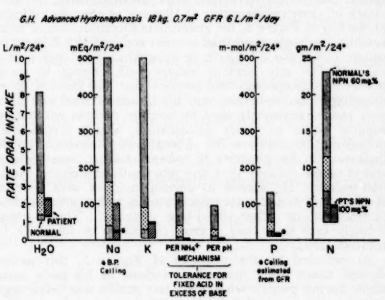

FIGURE 8. *Observations concerning the Residual Ranges of Homeostatic Capacity of G. H., a Ten-Year-Old Boy with Advanced Hydronephrosis (Case 3).*

The weight was 18 kg., the surface area 0.7 sq. meters, and the glomerular filtration rate 6 liters per square meter per twenty-four hours.

CASE 1 (Fig. 5). A 22-year-old man with chronic glomerulonephritis developed renal disease at 13 years of age. At the time of the present observations, measurements of inulin clearance showed his glomerular filtration rate to be 18 liters per square meter per day, or approximately 18 per cent of normal. Other information concerning his status is provided by the right hand of each pair of columns of Figure 5; the left hand of each pair, representing the normal data of Figure 4, is included for comparative purposes. A serrated upper or lower margin to the columns pertaining to the patient indicates that he has been observed to achieve equilibrium with the substance in question at the intake rate indicated without disturbing the corresponding physiologic key variable; in such instances it may be assumed that the physiologic limit lies beyond the level indicated. By contrast, a heavy black boundary line at the top or bottom of a column means that the subject has been observed or that he can with considerable certainty be expected to show an abnormal deviation in the physiologic key variable when taking the substance in question at rates in excess of those indicated by this ceiling or floor line.

It may be seen that this man was able to vary with impunity his intake of water and sodium over the ranges ordinarily used by normal persons. Moreover, he could stand at least an average potassium intake without getting into difficulty. On the other hand, his capacity to eliminate phosphorus† was limited to such an extent that he was liable

†This was estimated on the basis of the fact that the maximum rate of urinary phosphorus output of persons with intact parathyroid glands is equal to glomerular filtrate phosphorus content,[31,35] which may be calculated by multiplying glomerular filtrate volume times serum inorganic phosphorus concentration. In making this calculation in this patient, the upper limit of normal serum inorganic phosphorus concentration was taken as 5 mg. per 100 ml.

to hyperphosphatemia if he took an ordinary diet of generous phosphorus content. As revealed by the position of the serrated upper border of the diagonally shaded area, his observed range of phosphorus intake fell below this critical level. The pair of columns of the extreme right of this figure indicates there was a tendency for the nonprotein nitrogen concentration to be elevated to approximately 100 mg. per 10 ml.* when on a diet of moderate protein content.

As might be expected for a patient with such relatively minor limitations in homeostatic capacity, he was essentially free from metabolic disturbances while eating and drinking ad libitum. To minimize the risk of hyperphosphatemia and marked azotemia, however, he has been advised to avoid eating large amounts of meat, fish, milk solids or other foods of high phosphorus and protein content. Happily, this meant but minor restrictions for him.

CASE 2 (Fig. 6 and 7). A 21-year-old man with chronic glomerulonephritis developed renal disability after an acute attack of glomerulonephritis at 18 years of age. As indicated at the top of Figure 6, his glomerular filtration rate as measured by inulin clearance had become reduced to 6.8 liters per square meter per 24 hours, or approximately 7 per cent of normal. His safe working ranges with respect to water, potassium, phosphorus and protein also had become so reduced that he could not vary his intake of food and fluids over ranges commonly used by healthy persons without becoming liable to water intoxication, water insufficiency, potassium intoxication or phosphorus intoxication. No limitation in his capacity to tolerate sodium was observed and it seems unlikely that any practically significant limitation existed. He tended to develop acidosis with lowering of his serum bicarbonate concentration unless given sodium bicarbonate or other fixed-base therapy. This suggests strongly that there was a gross limitation in tolerance for acid-ash diets.

As revealed by the triangles of Figure 7, this patient showed much more marked deviations in his body water status during periods when his water intake was being regulated by physicians (left-hand data) than when he was permitted to take water according to his sense of thirst (right-hand data). Similar findings have been obtained on another patient (black circles), whose limits of water tolerance were equally reduced. In keeping with his observed limitations, he was advised to take water when thirsty and to take a diet of unlimited fat and carbohydrate content, but restricted to approximately 19 gm. of protein, 30 millimols of sodium, 18 millimols of potassium and 8 millimols of phosphorus per square meter per day. Fixed base was given in the form of calcium lactate in a dose of 4 gm. per square meter per day.

On this regimen he was essentially free from deviations in metabolic status other than the expected degree of azotemia for a period of 2 years. However, he suffered also from anemia and peripheral neuritis of gradually increasing severity. As a result of all these difficulties, he died during the subsequent year.

CASE 3 (Fig. 8). As indicated in Figure 8 the glomerular filtration rate of this 10-year old boy with atonic bladder, marked hydronephrosis and chronic pyelonephritis secondary to myelomeningocele amounted to approximately 6 liters per square meter per day, or 6 per cent of normal. The columns of the figure disclose the extent of limitations in his capacity to vary intake of water, potassium, fixed acid in excess of base and phosphorus without exceeding his residual homeostatic ranges. He could take relatively sizable amounts of sodium without becoming edematous, though not without becoming markedly hypertensive.

During the years preceding these approximate definitions of his specific limitations in homeostatic capacity, this boy at various times became water, potassium, chloride and phosphorus intoxicated, hypertensive, acidotic and rachitic. Since the institution of a diet designed to provide him with water and minerals at rates falling within his residual safe working ranges, he has been essentially free from all the difficulties mentioned above except water intoxication. This recurred on 2 occasions as a result of failure to take into account, in computing his obligatory fluid intake, the water content of solid and semisolid foods and the water used to wash down medications such as calcium lactate. Appropriate attention to these factors has prevented further recurrences of this difficulty. Though his skeleton is deformed, the rickets has become quiescent both as viewed roentgenographically and as evidenced by his serum calcium, phosphorus and alkaline phosphatase concentration values, which are at normal levels. His blood nonprotein nitrogen remains in the range of 80 to 120 mg. per 100 ml. This is in accord with the expectations set forth above in Figure 4.

This boy lives a moderately active and quite happy life. Though the neurologic malformations make it difficult for him to walk easily, he rides a tricycle with considerable vigor.

CASE 4 (Fig. 9). Measurements of inulin clearance showed the glomerular filtration rate of this 11-year-old boy with chronic pyelonephritis secondary to congenital disturbance in bladder-neck control to be about 3.5 liters per square meter per 24 hours, or less than 4 per cent of average normal values at the time of these studies. As might be expected under such circumstances, this patient has been observed to suffer from disturbances in water, potassium, acid-base, phosphorus and calcium homeostasis as well as from marked azotemia. As revealed by the left-hand column of Figure 9, his minimum water needs were markedly increased both because of a loss of ability to form a highly concentrated urine and because his rate of solute output was relatively high. At the same time, maximum capacity to eliminate water, which probably amounts to 2300 ml. per square meter per day, or less,† has resulted in water intoxication on a number of occasions.

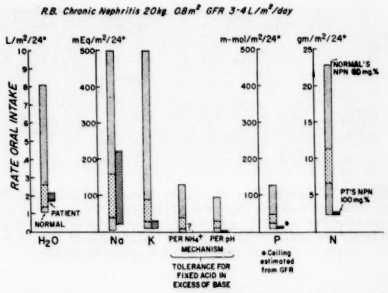

FIGURE 9. *Observations concerning the Residual Ranges of Homeostatic Capacity of R. B., an Eleven-Year-Old Boy with Chronic Pyelonephritis and Hydronephrosis (Case 4). The weight was 20 kg., the surface area 0.8 sq. meters, and the glomerular filtration rate 3-4 liters per twenty-four hours.*

It is of interest that he could vary his intake of sodium throughout and beyond the range ordinarily used by normal persons without becoming either dehydrated, edematous or hypertensive. The highest observed output rate (220 milliequiv. per square meter per day) amounted to about 45 per cent of his glomerular filtrate sodium content (about 500 milliequiv. per square meter per day). His capacity to excrete sodium at such a rate without difficulty probably was due in part to the fact that his serum albumin concentration was within normal limits (4.9 gm. per 100 ml.).

*Although this level has been set as the upper limit of "normal," it should be considered an arbitrary value, having little physiologic significance in terms of body economy.

†This theoretical estimate is based on the fact that maximum urine volumes rarely amount to more than 50 per cent of glomerular filtrate volume, suggesting that his maximum urine volume would not amount to more than 0.5 × 3500 ml., or approximately 1700 ml. per square meter per day. Assuming an insensible water loss of 800 ml. and a water of oxidation gain of 200 ml. per square meter per day, his over-all tolerance for water may be estimated to be 1700 + 800 − 200 or 2300 ml. per square meter per day or less.

This patient has not been observed to develop potassium intoxication probably because his rate of potassium intake has been restricted in accordance with estimates of his maximum capacity to excrete potassium.* On the other hand, he has been found hypokalemic at a time when he was suffering from hypocalcemia, hyperphosphatemia and metabolic acidosis. These findings indicate gross reductions in capacity to conserve body stores of fixed base by the ammonium ion and phosphate buffer mechanisms as well as a marked limitation in ability to eliminate phosphorus by physiologic means. In association with the latter disturbances, roentgenograms disclosed active rickets.

Though the data outlined above indicate that his capacity for homeostasis was so limited in certain respects that he could not take an ordinary diet without getting into difficulty, they also reveal that with the possible exception of phosphorus he should be able to take essential nutrients in amounts sufficient to meet minimum maintenance needs without suffering metabolic disturbances.

In accordance with this thesis, he was allowed to take calories as desired in the form of plain carbohydrate and fat. Protein was provided at ample maintenance levels (32 gm. per square meter per day), with the realization that it would result in moderately marked azotemia. To permit him to accomplish water concentration homeostasis by taking water in accordance with thirst, the water content of his basic regimen was kept below minimum maintenance levels (that is, at about 550 ml. per square meter per day), and he was told to drink plain water or ginger ale (which contains few fixed solutes) as indicated by his sense of thirst. Dietary sodium intake was at a high normal level (140 millimols per square meter per day). Dietary potassium was restricted to low maintenance levels (37 millimols per square meter per day). The intake of phosphorus was set at a level (17 millimols per square meter per day) that lay close to his maximum tolerance as set forth in Figure 9. To compensate for his presumed inability to conserve body stores of fixed base, 20 to 30 milliequiv. of the sodium per square meter per day was given as the bicarbonate. Additional fixed base was provided in the form of calcium lactate (7 gm. per square meter per day); 10,000 units of vitamin D was given to facilitate the absorption of this calcium from the gut.

Since the institution of this therapeutic program, he has maintained his weight satisfactorily and has been free from all the various metabolic disturbances mentioned above except hyperphosphatemia and rickets. At the time of this writing attempts are being made to adjust phosphorus intake so that the phosphorus needed to heal the rickets is made available while phosphorus overloading and hyperphosphatemia are avoided. As mentioned above, this patient's "safe working range" for phosphorus is so narrow as to make accomplishment of this goal exceptionally difficult.

Discussion

It has long been known that patients with marked limitation in kidney function may need to restrict the intake of certain foodstuffs and augment that of others if they are to avoid serious metabolic disturbances. The data set forth above show how these limitations may be expressed in at least approximately quantitative terms. They also illustrate how information concerning residual ranges of homeostatic capacity can be used as a basis for providing patients with their essential nutritional requirements in a physiologically tolerable manner.

As outlined above, one can determine whether an observed rate of urinary water or solute output is below, within or above the physiologically tolerable or "safe working range" by ascertaining whether the corresponding "physiologic key variable" is below, within or above normal limits. Up to the present time, no procedure has been devised that permits one to define all a given person's safe working ranges of intake in a simple, easy manner. On the other hand, much useful information can be had by measurement of rates of urinary output of water and solutes when the patient is first seen or while he is eating in his customary manner and considering them with relation to his homeostatic status at that time. Rates of output observed when the corresponding physiologic key variable is within normal limits indicate rates of input that should be tolerated satisfactorily. Contrariwise, rates of ouput observed under circumstances when the physiologic key variable is outside normal limits provide a point of reference for finding rates of intake that will permit the patient to regain metabolic normalcy. In addition, it seems reasonable to expect that as knowledge increases it will gradually become possible to predict, from some common denominator, limits of tolerance for water, potassium and so forth in the manner that phosphorus tolerances now can be predicted from glomerular filtration rate[21] and minimum renal water needs from solute output and glomerular filtration rate.[38]

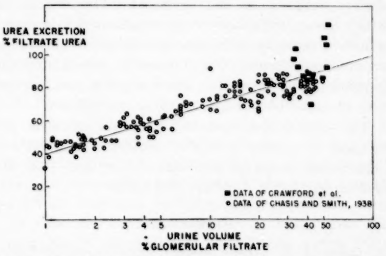

FIGURE 10. *Relation between Urea Clearance and Ratio of Urine Volume to Glomerular Filtrate Volume in a Normal Man and in Subjects with Glomerulonephritis (Data from Chasis and Smith[39] Supplemented by Unpublished Data of Crawford (et Al.)*

In the introductory comments, mention was made of the possibility of utilizing therapeutic regimens that will tend to augment a patient's tolerance for one or more dietary constituents. For example, it is known that urea clearance by the kidney may be augmented by an increase in urine volume relative to glomerular filtration rate (Fig. 10).[39] Similarly, tolerance for water may be augmented by the provision of a generous solute intake.[7] Moreover, renal capacity to eliminate potassium may be facilitated by elimination of body sodium deficits.[31]

It is to be hoped that further exploration of such interrelations will indicate a number of ways in which

*It has been assumed that the kidneys can excrete at least as much potassium as is contained in the glomerular filtrate,[36,41] which in this boy amounted to approximately 18 milliequiv. per square meter per day.

the tolerance ranges of nephritic patients for certain nutrients can be increased.

Although the provision of food and fluids at rates falling within residual ranges of homeostatic tolerance may enable severely handicapped patients to avoid certain types of metabolic disturbance and to live longer than they might otherwise be able to, it cannot be expected to correct the renal lesion itself. As exemplified by recent experiences with nephrotic patients undergoing long-sustained cortisone therapy, it may be possible to exert such a basically beneficial influence by hormonal or other means at least in certain cases. It is hoped that the procedures outlined here, by lessening metabolic disturbances and prolonging life, may contribute to the ultimate goal of accomplishing corrective therapy for patients with severe homeostatic disabilities.

Summary and Conclusions

Studies designed to eliminate at least in part some of the guesswork ordinarily involved in the management of patients with gross limitations in homeostatic capacity resulting from severe renal disease are reported. To provide a background against which to view the problems posed by such persons, normal limits of tolerance for water and certain important dietary constituents are reviewed. The degrees to which these limits have become narrowed in 4 representative patients with pannephritis are indicated in approximate terms. The manner in which such information may be used in the correction and prevention of metabolic disturbances is exemplified.

The experiences recorded here suggest that this method of approach to the problems in metabolic homeostasis posed by patients with severe renal disease is worthy of further exploration.

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MEDICAL INTELLIGENCE

NONGONOCOCCAL URETHRITIS IN MALES*

Report on 50 Cases Treated with Tetracycline

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B. G. CLARKE, M.D.‡

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DURING the period from May, 1954, to January, 1956, tetracycline§ has been available for clinical trial in the Genitourinary Clinic of the Boston Dispensary. Fifty patients with nongonococcal urethritis have been treated and returned for observation. Results have been good enough to warrant continued trials of the drug and presentation of the experience thus far obtained.

MATERIAL AND METHODS

All 50 patients were men with urethral discharge whose smears and cultures for gonococcus were negative. Serologic reactions for syphilis were negative in each case, as were urinalyses with the exception of findings of microscopic pyuria in the majority of cases and traces of albumin in a few.

Cultures for organisms other than *Neisseria gonorrhoeae* were made in 19 cases. Staphylococci were found in 18 of these. *Staphylococcus albus* was isolated in pure culture in 6, with diphtheroids in 10, with *Streptococcus viridans* in 1 and *Alkaligenes faecalis* in 1. Diphtheroids alone were reported in 1 case.

In 13 patients from whom *Staph. albus* was isolated in culture, the organism was tested by the disk method against tetracycline. It was sensitive, in vitro, to tetracycline in 11 and resistant in 2 of these patients. Both the last 2 patients were nevertheless cured by administration of the drug; 7 of the 11 tetracycline-sensitive strains of staphylococcus were tested against sulfadiazine and sulfisoxazole,¶ 6 of which were resistant to each drug.

The patients ranged in age from eighteen to fifty-five years, with an average of thirty-four years; 32 patients gave a definite history of genitoinfectious exposure. In these cases the incubation period ranged from one to ninety days. The average was sixteen days. The average duration of urethritis before treatment was nine days.

The standard course of treatment was 250 mg. of tetracycline orally four times a day for five days. Five patients were given total dosages in excess of this, ranging up to 9.25 gm.

RESULTS

Good therapeutic results were obtained in 48 of 50 cases. In every case, except the 2 failures, discharge was absent at re-examination within two to ten days. In most cases it had disappeared in three or four days. Two cases were rated as failures: 1 man exhibited persistent urethritis at seven days, and another at 4; neither submitted to retreatment or returned for further observation.

No untoward reactions to the drug were observed.

DISCUSSION

The preponderance of *Staph. albus* as an identifiable urethral invader in nongonococcal urethritis among the patients studied bacteriologically parallels the experience of others.[1,2] Penicillin is recognized as having limited utility in the management of this type of infection although in combination with streptomycin it has been found to have distinct value.[3,4] Recent experience in the armed forces[3] suggests that the sulfonamides may have considerable value in the treatment of nongonococcal urethritis. During the last decade, however, sulfonamides have been of progressively decreasing usefulness in the treatment of nonspecific urethral infection among patients seen at the Boston Dispensary. It is probable that the epidemiologic character of the disease varies from one locality to another.

Chlortetracycline[2] and oxytetracycline[3,4] have recognized usefulness, when orally administered, in the control of nongonococcal urethritis. It seemed advisable, with the appearance of another powerful antibiotic of apparently low toxicity,[5] to appraise its value to whatever extent was possible with the patients available. Oral administration of the tetracycline group of antibiotics for this disease has the great advantage of convenience for the attending physician in the clinic. Unfortunately, it is expensive, and certain patients cannot be depended upon to use the medication regularly. Urethral instillation of sterile antibiotic solutions has the virtue of economy in the use of relatively small quantities of drugs but the handicap of producing, in some cases, considerable local discomfort. In addition, urethral instillation requires special equipment and considerable expenditure of time by physicians or technicians in

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§Kindly supplied as Achromycin by Lederle Laboratories, Pearl River, New York, and as Tetracyn, by Pfizer Laboratories, Brooklyn, New York.

¶Available as Gantrisin from Hoffmann-LaRoche, Incorporated, Nutley, New Jersey.

the clinic. Ferguson, Miller and Herrmann[1] were able to show, in a large-scale study, that oxytetracycline administered topically is effective in over 97 per cent of cases with nonspecific urethritis. Similar results have been obtained with the topical administration of chlortetracycline.[6]

Summary

Tetracycline was administered orally to 50 patients with nongonococcal urethritis. Favorable results were obtained in 48. The normal dose was 250 mg. four times daily for five days. No untoward reactions to the drug were observed.

We are indebted to Drs. Harry Chaimson, Harry Golden and Hovnan N. Tashian for clinical co-operation, to Miss Anne P. Handley, R. N., and Mrs. Leslye Turrell for clerical assistance and to Miss Marilyn Ann Holmes and the late Mr. Abraham Abrahams for aid with the bacteriologic studies.

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DOCTORS AFIELD

Sir Ronald Ross

Don R. Lipsitt, M.D.*

Bronx, New York

THE chasm between the sciences and the humanities is accentuated by anxious attempts to unify the disciplines and to imbue the premedical student with a happy blend of liberal education in arts and sciences. And often a glance is cast longingly back to the days when the physician was also the scholar of the community. Blessed is the scientist who can now and again escape the islands of specialization and be part of the universal mainland, who can descend his ivory tower and count himself among humanity. Such a man was Ronald Ross, physician, scientist, poet, novelist, mathematician, musician, publicist and editor.

The first of ten children, Ronald Ross was born in Almora, India, on May 13, 1857. He was educated in England, where he lived with his cultured physician uncle, in whose library he encountered Don Quixote, Robinson Crusoe and Doctor Faustus. He became as conversant with the habits of frogs, fishes and birds as with the works of Shakespeare, Marlowe, Pope, Milton and Hume. And in the doctor's home he spent many happy hours singing, playing, painting, drawing or simply daydreaming. In his *Memoirs*, Ross[1] gives the following account:

> I was really not keen to do anything and was therefore probably an uninteresting pupil. My mind was mostly engrossed with dreams . . . I did things merely to pass the time and absolutely without any conscious desire to become accomplished in any line.

Having placed first in a national examination in drawing at the age of seventeen, Ross had thought of becoming an artist, but succumbed finally to his father's urging to enter the medical profession and ultimately the Indian Medical Service. He recalled:

> I resigned myself to this scheme, especially because it would give me experience of life in India, with shooting and riding and also a knowledge of biology and considerable leisure for any other hobbies I might have a mind for. But I had no predilection at all for medicine . . . and even felt disposed to look down upon it.[1]

And with this flimsy motivation for a medical career, he entered St. Bartholomew's Hospital on October 1, 1874. Here, except for a few close friends, "who worked harder than I did and became good students really interested in medicine, which I never was,"[1] he found a much coarser stratum of society than he had been used to. Nonetheless, he found medical studies tolerably acceptable as a potpourri spiced by the playing of piano and flute, the composition of lyrics and sonatas, the study of harmony and form, and the indulgence of an urge to paint and sketch. In 1879 he graduated, with the paradoxic realization that the medical profession and all its associates and associations were little to his taste or inclination, though he held in high esteem the magnificence of medical discoveries such as Lister's. (At this point, he was, indeed, a doctor afield.)

Failing his first attempt to qualify for the Indian Medical Service, Ross put to sea as a ship's surgeon, but finally achieved his objective in September, 1881. He was commissioned as surgeon and sent to India, where, as he had anticipated, Service obligations provided time for writing new works and revising old. He worked on his novels, composed music for several of Shelley's lyrics and diligently pursued the world's poets in German, French and Italian. It was at this time that he versified the prophetic thoughts that would subsequently carry him over the cobbled path of rigorous scientific inquiry:

> O Heaven, shall man rebelling never take
> From Fate what she denies, his bliss?
> Cannot the mind that made the engine make
> A nobler life than this?[1]

Ross was shuttled about India, filling the frequent gaps in a great governmental jigsaw puzzle, but remained a contented government employee as long as his proclivity for writing was not thwarted. Evidence abounds that his whims were not obstructed: he pampered his passion for music by taking an old piano on his travels or plaguing his colleagues with

*Intern, Bronx Municipal Hospital.

practice on the violin; his meditations and reflections found expression in an essay on Wordsworth, a short story called "The Vivesector Vivesected," a novel, *The Spirit of Storm,* whose subject matter was a variation on the Pygmalion theme, a comedy drama called *"The Misanthropes,"* which deals with modern life in Elizabethan style, and another novel, *The Child of Ocean,* which one critic of the day compared favorably to Stevenson's *Treasure Island.*[2] Many poems were born between the longer works. His inventive mind contrived phonetic shorthand systems, toyed with the hypothesis that all concepts were definable in terms of the three entities, space, matter and motion, and derived a system of operative algebra that has become incorporated into more modern mathematical systems. In later years Ross devised some of the earliest epidemiologic statistical concepts in the quantitative study of parasitic invasion and infection in individuals and groups; to this study he applied the term "pathometry." Withal, there was time and energy for enthusiastic participation in polo, lawn tennis, sailing and the native delights of riding, hunting and shooting. But his pleasure-bound days were stalked by the villain conscience, and he was painfully reminded of his obligation to medicine and mankind; he was suddenly aware of a delinquency and ineffectuality, and his resultant perplexity reflects in the following statement:

> I did not decry either literature or mathematics or music for this purpose; but I was a doctor and the voice from within answered:
>
> Abandon Wrath and Ruth.
> Touch not the High, nor ask.
> For God alone the Truth.
> Perform thy daily task.[1]

Ross returned to England to contemplate his plight with perspective and was soon caught up in the excitement of Koch's and Lister's new theories. His curiosity was piqued, and he was driven to study the new science of bacteriology, which netted him a diploma in public health and a considerable knowledge of the most recent technics in microscopy, incubation, and preparation of culture mediums. With these scientific acquisitions and his outlook on life somewhat refurbished by rest, travel and study, Ross again was India bound, but the smoldering embers of his earlier discontent were soon again fanned to flame. He earnestly considered the professional pursuit of literature and again sought resolution of his uncertainties in his writings. In a stanza of a poem called "Duty," he seemed ready to "ride the whirlwind and direct the storm":

> Under the granite arch
> Of Duty, spann'd above,
> Out of ourself we march
> Away from life and love.[2]

In Ross's words, he "lived in mist and waited for something,"[1] but perhaps the mist was to clear sooner than he expected, for in September, 1894, he made the climactic acquaintance of Dr. Patrick Manson in London. Well versed in parasitologic technic through his work with filaria, Manson was to direct Ross down the road of success. Before returning to India to begin the search for the critical needle in the scientific haystack, Ross consolidated his gleanings from Manson and the literature in an essay on the problems of malaria, which earned him the Parkes' Memorial Gold Medal Award and 75 guineas. Limited space cannot do justice to the drama and hardship that led to the day in August, 1897, when Ross finally saw in the stomach of the Anopheles mosquito the pigment-laden, delicate, circular cells that were the malaria parasites. In his notebook, on that day, he wrote (in part):

> Seeking his secret deeds
> With tears and toiling breath
> I find thy cunning seeds
> O million-murdering death.
> I know this little thing
> A myriad men will save.
> O death where is thy sting?
> Thy victory, O grave?[4]

Ross had found his grail and had given the world the answer to one of medicine's most baffling problems. Yet he continued to propagate his knowledge as the first lecturer on tropical medicine in the Liverpool School and later as editor of the periodical *Science Progress.* And for his achievements and contributions, he was awarded the Nobel Prize in Medicine in 1902, and the British Government gave recognition and patronizing apology for earlier apathy by knighting him in 1911.

Throughout his life, his fecund imagination fed voraciously on all provender and was ever molding the raw resources of life and the morbid misery of disease and death into forms that would lighten the woes of the world. Although his literary creations were often in the penumbra of his more notable scientific discoveries, critics of his day held Ross in high esteem as a man of letters, and critics of the present day can certainly envy his refusal to enthrone science as the only deity the human mind could recognize.

In his declining years, Ross was haunted by the specter of poverty. On September 17, 1932, at the age of seventy-five, he died in his own memorial at the Ross Institute in London, a laboratory and hospital founded by the Prince of Wales for the study and treatment of tropical diseases. During the same year, friends and admirers had initiated a subscription fund to assure Ross a carefree old age. It never came to use.

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42401

PRESENTATION OF CASE

A sixty-four-year-old man entered the hospital because of abdominal tenderness.

Two and a half years previously a right-sided colectomy, with an end-to-side ileotransverse colostomy, was performed because of a mucocele that replaced the appendix and extended from the lower pole of the right kidney to the pelvis. The lesion was broken into during the procedure. No other abnormalities were noted. The patient was well until one year later, when there were episodes of vague, fleeting abdominal pain in the right lower quadrant. Lower abdominal tenderness, especially on the left side, was noted at this time. A barium-enema examination demonstrated a well circumscribed filling defect that measured 1 cm. in diameter in the region of the anastomosis; diverticula were noted in the descending and sigmoid colon. Sigmoidoscopic examination showed mucosal injection. A year before admission the patient experienced pain in the lower abdomen when straining at stool. A tender, somewhat movable abdominal mass that measured 5 cm. in diameter was palpable in the mid-line below the umbilicus. An abdominal film showed a large quantity of fecal material and gas. A barium-enema examination demonstrated no definite lesions except for the previously noted diverticula. The patient refused operation. Subsequently, he remained well until one month before entry, when he noted soreness in the right lower quadrant of the abdomen that was accompanied by sharp jabs of pain whenever he was subjected to a bumping motion. Two or three weeks before admission there was diarrhea, with some bright-red blood noted in the stools. Proctoscopic examination showed an extracolonic "shelf" but no intrinsic lesion.

Five months previously there was an episode of pneumonia involving the left lower lobe that was successfully treated with antibiotics. He had had hypertension for many years. There was a past history of alcoholism.

Physical examination showed a well nourished man. The optic fundi showed arteriovenous nicking and tortuosity. The heart was not enlarged. Examination of the abdomen revealed a smooth, hard, tender, mobile, nonpulsating mass in the mid-line, just inferior to the umbilicus, that measured 7 cm. by 15 cm. There was a healed transverse surgical incision in the right lower quadrant. Peristalsis was normal. The edge of the liver, which was firm and tender, was felt 3 fingerbreadths below the right costal margin. There was a smooth, hard, nontender mass measuring 3.5 cm. in diameter in the edge of the liver just lateral to the rectus muscle. The spleen was not palpable. Rectal examination showed slight prostatic enlargement and a rubbery rectal "shelf" anteriorly. The peripheral pulses were normal.

The temperature was 98.6°F., the pulse 72, and the respirations 20. The blood pressure was 205 systolic, 110 diastolic.

FIGURE 1.

The urine was normal. Examination of the blood revealed a hemoglobin of 14 gm. per 100 ml. and a white-cell count of 8600. The nonprotein nitrogen was 26 mg., the bilirubin 0.9 mg., the total protein 7 gm., and the fasting blood sugar 97 mg. per 100 ml. The prothrombin content was 70 per cent, the cephalin flocculation +, and the bromsulfalein retention 2 per cent. A stool specimen gave a negative guaiac test. X-ray films of the chest showed tortuosity of the aorta. A barium-enema examination showed irregu-

larity at the anastomotic site; the terminal ileum was displaced laterally to the right by an extrinsic soft-tissue mass (Fig. 1). An intravenous pyelogram demonstrated normal kidneys; the ureters were not seen.

On the seventh hospital day an operation was performed.

Differential Diagnosis

Dr. S. Peter Sarris*: This sixty-four-year-old man, two and a half years before admission, had the right side of the colon removed, together with a huge mucocele replacing the appendix. In the next two and a half years, although he remained fairly well he had an enlarging mobile mass in the lower abdomen that did not produce many symptoms. Naturally, the first question to ask is, Was there any relation between the original operation and the present condition? The probability is that there was. Mucoceles of the appendix are infrequent, and a mucocele that "extended from the lower pole of the kidney to the pelvis" is rare indeed.

The symptoms do not help me in the differential diagnosis except in a negative way. The abdominal symptoms were fleeting and vague and were consistent with a mass of any type, malignant or nonmalignant. The pneumonia five months before admission, I believe, was irrelevant. The fact that the patient was well nourished is helpful; I have to concentrate on the types of tumors that can grow to this size and have little or no effect on the general condition of the patient.

The most striking finding was the large mass, 7 by 15 cm., just below the umbilicus, which was mobile, nonpulsating, tender and hard. The liver was enlarged and had on its edge a 3.5-cm., nontender, hard mass. The rectal examination indicated a rectal shelf, which apparently was not the typical one associated with metastatic seeding in the cul-de-sac from carcinoma of the stomach or bowel. That type of rectal shelf is nodular and hard; this was described as rubbery. There was no indication in the protocol whether the mass in the cul-de-sac was continuous with the one in the abdomen or separate from it. I suspect that it was separate because of the mobility of the one in the abdomen below the umbilicus. Then there are three masses to explain: one on the edge of the liver; one in the abdomen below the umbilicus; and one producing a rectal shelf.

The laboratory data help only in a negative way. There was no anemia; the white-cell count was normal, and, I assume, the smear was normal. The minimally elevated bilirubin, the + cephalin flocculation, the normal bromsulfalein retention and the slightly abnormal prothrombin content are not very helpful. The stool specimen gave a negative guaiac test, even though the patient had had some blood in the stools previously. I should like to review the x-ray films. There were three sets of films: one a year after the colectomy showing a filling defect in the anastomosis; one taken later, in which the filling defect was not mentioned; and one showing an irregular anastomosis with a large mass displacing the ileum to the right.

Dr. Frederick S. Tomchik: In the barium-enema examination done a year after the colectomy the colon appears to have been transected about through the middle portion of the ascending colon. The hepatic flexure is in place, and some colon proximal to that point remains. There is reflux into the terminal ileum, which is possibly a little dilated.

Dr. Sarris: Where is the small filling defect in the colon?

Dr. Tomchik: It is on the lateral wall of the ascending colon a few centimeters distal to the anastomotic site. It persists through subsequent examinations. A week later, in a plain film, the same small mass is outlined by air in the colon; some barium still adheres in its vicinity. A barium-enema examination one week later reveals a difference in the appearance of the region of the anastomosis; there is a bulge upward and a vague suggestion of the coiled-spring appearance that we associate with intussusception. It is possible that the anastomosis was intussuscepting slightly. The terminal ileum is slightly dilated, and there is apparently some fluid in it. In the year and a half before the operation finally mentioned in the protocol the small filling defect in the ascending colon is present and unchanged in appearance. The dilatation of the terminal ileum, however, is not evident. A barium-enema examination done a year after the one just mentioned shows no upward bulge in the region of the anastomosis. In the plain films taken on the last admission there is a suggestion of a new mass in the right lower quadrant that does not seem to correspond in size or position to the one in the lower abdomen found on physical examination. In other films the same mass is visible in the region of the terminal ileum. A barium-enema examination done that same day shows a normal-looking colon and considerable reflux into the ileum; at the most proximally visualized portion of the ileum is a rounded extrinsic pressure defect on the ileum, very likely from the mass seen on the plain films (Fig. 1).

Dr. Sarris: Mucoceles can be divided into two types, the benign and the malignant. The origin of the benign mucocele of the appendix is thought to be scar-tissue formation at the base of the appendix after a mild inflammatory attack, with stenosis of the area and complete closure at its base; the continued secretion of mucus from the lining of the appendix into the lumen then forms a mucocele. These can be of any size, from 2 or 3 cm. up to the size described here. They have a perfectly smooth lining and are eliminated by removal of the appendix.

The malignant mucocele differs not at all in external appearance from the benign mucocele. Its

*Clinical associate in surgery, Massachusetts General Hospital; chief of surgery, Union Hospital, Lynn; associate chief of surgery, Lynn Hospital.

lining, however, has papillary projections. It is really a low-grade adenocarcinoma. The malignant one, if it ruptures spontaneously, as it sometimes does, or is ruptured during an operation, seeds over the peritoneum, and the condition called pseudomyxoma peritonei occurs. It will implant on the liver surface and in the cul-de-sac — in fact anywhere in the peritoneal cavity — and continue to secrete the mucous material and form masses everywhere. The size of the mucocele in the patient under discussion would favor a malignant, rather than a benign, mucocele. I think pseudomyxoma peritonei best explains the entire picture. This man had a mucocele that was ruptured during its removal, and in the next two and a half years he had abdominal masses consistent with pseudomyxoma peritonei. He was not very sick, which is also characteristic of this condition. For the size of the tumor, pseudomyxoma is less likely to affect the patient systemically than a carcinoma originating, for example, in the bowel.

In these conferences double and triple diagnoses are not uncommon, so that I think I must discuss the possibility of two diseases — the second of which would be totally unrelated to the mucocele. Abdominal lymphoma can produce a rectal shelf, a hard mass on the middle portion of the abdomen and a mass on the edge of the liver. Several years ago I discussed a case* here in which there was a mass in the right lower quadrant, partially obstructing the terminal ileum, that was metastatic from a carcinoma of the gall bladder. The patient now under discussion had a hard mass at the edge of the liver, which could have been a primary carcinoma of the gall bladder. I believe, however, that he would have been sicker. He may have had cirrhosis of the liver; he had been a heavy drinker of alcohol in the past and he had an enlarged liver. Anyone who has cirrhosis is a candidate for hepatoma. The abdominal mass may have been a metastasis from a hepatoma. Again, I think he would have been sicker.

Although a primary carcinoma could have developed in the site of anastomosis, I do not like to consider a primary carcinoma of the gastrointestinal tract, for there is no evidence of it in the x-ray films — no ulcerations. A patient with primary carcinoma of the gastrointestinal tract, a mass of grapefruit size, a rectal shelf and a lesion in the liver, all produced by metastases, would have had more symptoms of obstruction than this man had. He was never nauseated or vomited; the only disturbance of bowel habit had been pain on straining at stools and occasionally diarrhea.

A large tumor that may displace the terminal ileum and cause metastases to the liver is carcinoid of the terminal ileum. Unlike carcinoids of the appendix, carcinoids of the terminal ileum metastasize fairly frequently, do produce large masses and do encroach on the ileum; size for size, they do not make the patient as sick as a primary carcinoma of the bowel would.

There is one other possibility of connecting the two diagnoses. Whenever a mass that is tender develops in a patient who has been operated on, one has to consider the possibility that a foreign body has been left behind at the time of operation. There was no mention of an opacity suggestive of a sponge in the x-ray report. A few years ago I had a case of an abdominal mass that was produced by several pieces of Oxycel left in the operative site to stop the bleeding. If this had been a foreign body there would have been more evidence of sepsis with an elevated temperature and a high white-cell count. Moreover, I do not think that the mass would have been so movable.

I could discuss other possibilities, such as neurogenic sarcoma, gumma and so on. Before I make the final diagnosis, I should like to know whether the mucocele was examined here and how it was classified.

DR. BENJAMIN CASTLEMAN: It was examined here and was a mucocele.

DR. SARRIS: My diagnosis, then, will have to be pseudomyxoma peritonei, started from a rupture of a mucocele of the appendix.

DR. CASTLEMAN: Dr. Nardi, will you tell us about the first operation?

FIGURE 2.

DR. GEORGE L. NARDI: At the admission during which the mucocele was removed this man had abdominal pain. A small mass was palpable in the right lower quadrant; the history and the physical findings were suggestive of acute appendicitis and that was our working diagnosis. Dr. Glenn E. Behringer, with all due credit, did suggest a mucocele. We operated on the patient with a preoperative diagnosis of appendiceal abscess. We found a mucocele, which extended to the lower pole of the kidney and filled the true pelvis. We had to divide the parietal peritoneum to excise it. In the course of the dissection the mucocele was ruptured.

*Case Records of the Massachusetts General Hospital (Case 34102). *New Eng. J. Med.* **238**:334-337, 1948.

Clinical Diagnosis

Peritoneal lymphoma.

Dr. S. Peter Sarris's Diagnosis

Pseudomyxoma peritonei.

Anatomical Diagnoses

Pseudomyxoma peritonei, with extension through the diaphragm to pleura. (Resection of mucocele of appendix, two and a half years before admission.)

Pathological Discussion

Dr. Castleman: Dr. Richardson, will you tell us about the second operation?

Figure 3.

Dr. George S. Richardson: The abdomen was loaded with myxomatous material — a real "jelly-belly" as it is described in the literature. The omentum was the large mass that was palpable in the abdomen; it was very thick and studded with gelatinous lumps. There were many other gelatinous nodules, including one in the region of the previous anastomosis. The process was not resectable at the time, and since there was nothing that we could do for the patient surgically, we merely took a biopsy of the omentum.

Dr. William H. Baker: After this operation I followed the patient for the last two years of his life in the Tumor Clinic. Originally, we received a pathological diagnosis of colloid adenocarcinoma and we treated him with tri-ethylene melamine, an oral alkylating agent. After three weeks of therapy, which resulted in a slightly lower white-cell count, we decided that the therapy was not effective and discontinued it. At that time the pathologists reviewed the slides and gave us the diagnosis that Dr. Castleman will talk about. We saw the patient periodically in the

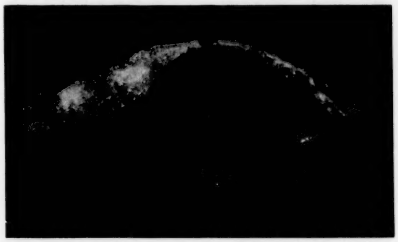

Figure 4.

Tumor Clinic without giving him specific therapy. In the last two years he went downhill, became slightly anemic, with a hemoglobin of 11.4 gm. per 100 ml., lost 27 pounds in weight and finally became very cachectic in the terminal phase.

Dr. Castleman: A year later he returned complaining of more abdominal pain and finally died. Peritonitis developed after another operation. At autopsy the loops of bowel were adherent to each other and covered with fibrin. There were nodules of jellylike material located over the peritoneum as well as over the surface of the liver. The omentum, which was the mass that was probably felt, was made up of semisolid gelatinous material (Fig. 2). Under the diaphragm was a mass of gelatinous tissue. The surprising finding, and it is the only case that I have been able to find or have read about in which this was found, was gelatinous nodules on the pleura and the diaphragmatic surface of both lungs (Fig. 3).

Dr. Baker: Is this consistent with direct extension to the diaphragm and pleura?

Dr. Castleman: I think that is what happened. The liver parenchyma was normal, but its surface was covered with mucoid material (Fig. 4). Microscopically, there were rows of epithelial cells lining islands of mucus. This is well seen in the section taken from one of the pleural nodules (Fig. 5). One of the theories of the etiology of pseudomyxoma peritonei is that it is merely a reaction of the serosa of the peritoneum that is stimulated by the mucocele and that it is not a true implantation. A discussion of this subject has recently been presented by Carleton.* I, per-

*Carleton, C. C. Mucoceles of appendix and peritoneal pseudomyxoma. *Arch. Path.* **60**:39-48, 1955.

sonally, believe that it is an implantation of material that originated in the appendix. Whether one wants to call this a colloid adenocarcinoma or pseudomyxoma peritonei really does not matter. It is a lesion that does not metastasize, if by this one means true embolic metastases. In the first operation Dr. Nardi inserted three fingers into the esophageal hiatus; at

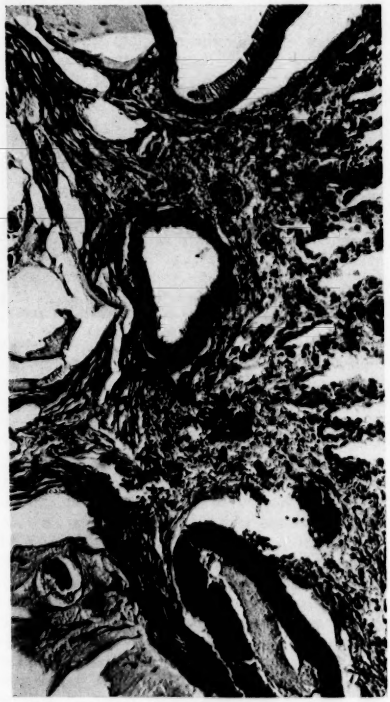

FIGURE 5. *Photomicrograph, Showing the Pseudomyxoma on the Pleura.*
Lung tissue is on the left, epithelial cells in the center, and myxomatous tissue on the right.

autopsy we could insert only one finger through it; there was myxomatous material all around it on the abdominal side. I think, perhaps, some of the myxomatous material permeated through the hiatus and started to grow on the pleural surface.

This may be a key case in refuting those who believe that this condition is a serosal reaction with the secretion of mucus. One could, I suppose, argue that the pleura could respond in the same way, but I think it would be farfetched. I should rather leave it with the same diagnosis than say it was a colloid adenocarcinoma, because I do not believe it would metastasize. If implantation denotes malignancy, it is malignant.

DR. RICHARDSON: The over-all survival of the patient from the first operation to death was nearly five years. Did you say that the mucocele does not metastasize, but just invades?

DR. CASTLEMAN: It was present on the surface of the lung and liver. I think it is analogous to the thymoma in the mediastinum, which implants over the pleura and pericardium and occasionally permeates through the diaphragm to implant on the surface of the liver, but does not metastasize embolically. The individual cells in pseudomyxoma peritonei look perfectly benign; there is very little, if any, atypicality.

CASE 42402

PRESENTATION OF CASE

A seventy-five-year-old man entered the hospital because of abdominal pain.

Three and a half months previously he noted persistent, aching, gradually worsening epigastric pain that was unrelated to meals and radiated diffusely over the abdomen. At another hospital an upper gastrointestinal series was normal, and a Graham test was negative. The pain was at first relieved with Bufferin, but this afforded less relief as the pain worsened. He was frequently awakened at night because of the pain. There was associated anorexia, occasional nausea and a loss of 23 pounds in weight. An episode of vomiting occurred one week before admission. During the week before entry the pain radiated to both sides of the back. There was no diarrhea, fever or jaundice. During the six months before admission he had been constipated. Slight transient relief of the epigastric pain occurred with a bowel movement. There was no melena.

During the six years before entry there were occasional episodes of mild, constricting, nonradiating substernal pain that were unassociated with exertion, lasted for a few minutes and were relieved with nitroglycerin. There was a history of three attacks of rheumatic fever between the ages of thirty-seven and forty-seven. Hypertension had been known to be present for six years. A gradually enlarging irreducible inguinal hernia on the left had been present for twenty-five years.

Physical examination showed a fairly well nourished, fatigued, elderly man. There was no lymphadenopathy. The chest was emphysematous. The left border of cardiac dullness extended 3 cm. to the left of the midclavicular line in the fifth intercostal space. A Grade 2, apical, systolic murmur was audible. Examination of the abdomen showed slight tenderness in the left epigastrium and an irreducible left inguinal hernia. Rectal examination revealed a slightly enlarged prostate that was neither nodular nor indurated.

The temperature was 99.4°F., the pulse 72, and the

respirations 18. The blood pressure was 200 systolic, 110 diastolic.

The urinary sediment contained 1 to 4 white cells and a rare red cell per high-power field. Examination of the blood revealed a hemoglobin of 12.8 gm. per 100 ml. and a white-cell count of 16,000, with 85 per cent neutrophils. The nonprotein nitrogen was 18 mg., the total protein 7 gm., the albumin 4.6 gm., the globulin 2.4 gm., the bilirubin 0.5 mg., and the fasting blood sugar 96 mg. per 100 ml. The alkaline phosphatase was 3.4 and 5.3 units. The prothrombin content was 67 per cent. Cephalin flocculation was negative. X-ray films of the chest demonstrated left ventricular enlargement. A Graham test showed a faintly outlined gall bladder that appeared to be normal in size and shape. An upper gastrointestinal series showed no intrinsic lesion of the stomach or duodenum except for a small hiatus hernia. There was slight extrinsic pressure on the lesser curvature and posterior wall of the stomach (Fig. 1 and 2). An intravenous pyelogram was normal, and barium-enema and sigmoidoscopic examinations were negative. An electrocardiogram showed first-degree heart block and questionably significant, nonspecific T-wave changes.

FIGURE 1. *Posteroanterior View of the Stomach, Showing Extrinsic Pressure on the Lesser Curvature.*

On the second hospital day the temperature rose to 103.2°F., and over the next six days it ranged between 99.4 and 103.6°F. A culture of the urine grew out a few *Staphylococcus albus*. Examination of the chest on the sixth hospital day revealed rales at both lung bases. X-ray films of the chest demonstrated blunting of both costophrenic angles, more marked on the left; there was a suggestion of some loss in volume of the left lower lobe. On the next day the patient appeared weaker, with episodes of confusion. Films of the chest showed, in addition to previous findings, platelike atelectasis just above the right-lower-lung field. A lumbar puncture yielded clear acellular cerebrospinal fluid under a pressure equivalent to 140 mm. of water; the protein was 65 mg. per 100 ml. A blood culture showed no growth. With Chloromycetin therapy the temperature and white-cell count

FIGURE 2. *Right Anterior Oblique Spot Film, Showing Extrinsic Pressure on the Posterior Wall of the Body of the Stomach.*

fell to normal, and the patient's mental status improved.

An operation was performed on the thirteenth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. JOHN D. STOECKLE*: A seventy-five-year-old man had persistent epigastric pain. Simple therapeutic measures and diagnostic studies did not help him or tell us what caused the pain. He was hospitalized for more detailed study.

Can we surmise the site of the disease from what he reported about the pain? Its location and radiation suggest an origin in the upper gastrointestinal tract, the gall bladder, or the structures in the retroperitoneum. Its failure to be influenced by food in any way makes the stomach and duodenum unlikely. Its persistence and aching quality do not remind us in any way of the variations of gall-bladder colic. The description is most in keeping with pain from the retroperitoneal pancreas or aorta — organs with a rich supply of nerves — or from enlarging retroperitoneal lymph nodes. The physical examination does not help

*Assistant physician, Massachusetts General Hospital.

locate the site of the abdominal disease but tells that the patient had hypertension with cardiomegaly and that he did not have a pulsatile aortic aneurysm. We have the interesting side story of three attacks of rheumatic fever after the age of thirty-seven. It can occur, as noted in the streptococcal epidemics in military service, but it is unusual; and I am sure none of the examining physicians thought the murmur reflected mitral valvulitis.

Nearly all diagnostic x-ray examinations of the abdominal contents were done. Dr. Hanelin will review the x-ray studies and tell us whether the patient had any findings of pancreatic or lymph-node disease.

DR. JOSEPH HANELIN: Findings of chief interest radiographically center themselves in the gastrointestinal films. The examiner found no obvious intrinsic lesion of the stomach, and that would appear to be the case from the film evidence also. However, there is a strong suspicion of a mass extrinsic to the stomach, which impresses the lesser curvature of the body and the posterior wall and which may result from a pancreatic or retroperitoneal tumor (Fig. 1 and 2). The pulmonary changes that occurred in the hospital — first abnormal density at the right base and later in the left lower lobe with obscuration of the costophrenic angles — strongly suggest pulmonary infarcts, with pneumonitis a lesser consideration.

DR. STOECKLE: The clinical chemist is not helpful with this diagnosis. If we might, for the moment, consider the pancreas the site of disease, he might have helped us with the diagnosis of acute pancreatitis, with serum amylase and lipase studies. Those, however, do not have comparable certainty in establishing the diagnosis of cancer of the pancreas. Other procedures, such as cytologic examination of duodenal contents and study of the duodenal enzymes after stimulation of the pancreas, add only slightly to one's clinical confidence in the diagnosis of cancer of the pancreas before the surgical exploration and are not precise aids in excluding it. On the basis of the information given, I suspect that this man had an abdominal exploration with a view to making the diagnosis.

The exploration, however, was delayed because he became sicker. The febrile course, the bilateral rales with pleural fluid, the later x-ray examination showing platelike atelectasis and the leukocytosis are all most consistent with pulmonary infarcts, in spite of the apparent response of the condition to Chloromycetin. This event strengthens the suspicions of carcinoma of the pancreas because of the incidence of thrombophlebitis associated with the disease — a presumed source for such pulmonary infarcts. Thrombophlebitis, of course, occurs in sick patients with other abdominal cancer and per se is not a sign of cancer of the pancreas, either symptomatic or asymptomatic. A recent review[1] dispels the view that thrombophlebitis is a common event in asymptomatic neoplastic disease. Although not common, phlebitis before clinically manifest local cancer does occur, its significance being obscure.[2]

I shall say that the patient had a retroperitoneal tumor, most probably cancer of the pancreas. That seems so straightforward that I hesitate to make it, but I find little else to consider, other than lymphoma.

CLINICAL DIAGNOSIS

?Lymphoma.

DR. JOHN D. STOECKLE'S DIAGNOSIS

Cancer of pancreas.

ANATOMICAL DIAGNOSIS

Adenocarcinoma of body and tail of pancreas.

PATHOLOGICAL DISCUSSION

DR. PAUL S. RUSSELL, JR.: Dr. Stoeckle is correct in suggesting that an important purpose of the operation was to establish a diagnosis. Exploration revealed a large, firm tumor of the body of the pancreas, with nodular extension to the tail of the gland. Although the head of the pancreas was a bit more firm than normal, there was no appreciable constriction of the ampulla of Vater — the common duct was about 8 mm. in diameter. One nodule, more accessible than the rest, presenting at the ligament of Treitz along the inferior border of the pancreas, was biopsied. This was reported to contain adenocarcinoma on frozen section. The extent of the lesion, particularly its circumferential distribution around the superior mesenteric vessels, led us to decide against any form of ultraradical resection. The absence of any suggestion of bile-duct obstruction likewise argued against side-tracking the biliary drainage, so nothing further was done.

We were quite interested in this patient's febrile course before operation, culminating in the rise in temperature to 103.2°F. Its dramatic response to Chloromycetin is the sort of thing we are accustomed to see in cholangitis, which is common enough as a secondary phenomenon in carcinoma of the pancreas associated with biliary obstruction. But in this case there was no biliary obstruction. Perhaps this could have been a similar sort of infection involving the partially obstructed pancreatic-duct system without the accompanying enzymatic digestion that we usually associate with pancreatitis.

DR. LEONARD ATKINS: The biopsy specimen that we received showed an adenocarcinoma that was consistent with pancreatic-duct origin. The patient left the hospital on the ninth postoperative day. He is still living four months later, is anorectic, eats very little and is losing weight. He has only occasional epigastric pain, which is relieved by Demerol.

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PHYSICIANS PER POPULATION

BETWEEN 1910 and 1930 the population of the United States increased at the average rate of about 1.5 per cent a year whereas the number of physicians increased each year by less than two thirds of 1 per cent. However, between 1930 and 1950 the rate of physician increase more than doubled, at an average of 1.4 per cent a year, whereas the population increase fell off slightly, to just a little more than 1 per cent. During the past decade (1945 to 1955) population has increased at the average rate of 1.9 per cent a year, and the number of physicians at the average rate of 1.8 per cent.

It must be pointed out that an increase in population of 1 per cent annually means at the present time an increase of 1,678,580 persons each year. A corresponding increase of 1 per cent in the number of physicians would amount to 2181 new doctors each year. This number would be required to maintain the present ratio of 1 physician to 769 persons. In 1930, on the other hand, a 1 per cent increase in population meant 1,228,000 persons, and 1550 new physicians a year would have met the requirement of a corresponding increase in the number of physicians as of that time.

During the past ten years the annual requirement of new physicians (roughly 2 per cent — that is, twice 2181, or 4362) seems to have been easily covered by the graduation of 6000 or 7000 doctors each year (the approximate annual output of the present 75 medical schools that offer a full four-year course of instruction).

The country is now confronted with the almost unbelievable fact, according to a statement contained in the recent annual report of Dr. Willard C. Rappleye, dean of the Faculty of Medicine at Columbia University (who is undoubtedly adequately informed), that more than 5000 foreign physicians will enter the United States this year. Many of these physicians are visiting this country to obtain training as interns, residents or holders of fellowships, and just how many of them will be admitted to practice is difficult to guess. According to Dr. Rappleye 25 to 50 per cent of the house staffs in the hospitals of the United States are aliens, a good proportion of whom would probably be delighted to remain here after completing their training, although many of them will be unable to do so because of restrictive state laws.

It is desirable that these facts and statistics should be generally known. Hastily conceived proposals that the number of medical schools be immediately increased, or that present medical schools be expanded without regard for their ability to obtain adequate teaching personnel must be carefully considered if the process of matching the increase in population with an adequate number of properly trained physicians is to be as rational and orderly as possible.

PRESSORECEPTIVE AGENTS

THE *Boston Herald*, in its issue of August 30, 1956, published an editorial comment in regard to the propriety of the Massachusetts Legislature's action of 1949 relative to hypertension. The conclusion seemed to be that, whereas the action of the Legislature was consistent with the finer instincts of humanity, there may be a legitimate doubt whether the indulgence of these instincts by the lawmakers of the Commonwealth, acting in their official capacity, was in this instance entirely consonant with the purposes for which they were elected.

The reason for this particular legislative action, which may now have been forgotten by a majority of those who were originally interested by it, resulted, it has been said, from the illness of a respected member of the General Court. This unfortunate circumstance brought the importance of the problem that it represented to the attention of the Legislature, which forthwith established a recess commission to investigate the disorder. Three years later the papers comprising a symposium on essential hypertension were published, and now, seven years later, the Commission, renewed each year, has produced a 3-volume report of considerable merit containing presumably all that is presently known about the disease. Available to any prospective purchaser at the cost of publication, the text represents a $197,000 gratuitous and involuntary gift from the taxpayers of Massachusetts to the world at large.

Since medical textbooks are on the road to obsolescence from the date of publication, the major recommendation of the Commission — that a permanent commission on hypertension be established — is as logical as its original establishment was illogical.

Complete consistency should perhaps now dictate the appointment of similar commissions on arthritis, cancer, diabetes, mental illness and the acute infections with special reference to the adenoviruses, or even the establishment of the State's own baby institutes of health, to match, in a small way, those that operate under the auspices of the federal Department of Health, Education and Welfare.

With all due respect to the practical value of this admirable presentation of the facts about hypertension there is another aspect of the situation that carries its own educational revelation — the apparent ease with which tax money can be dissipated by those who have the authority to levy and the power to spend it.

SCHOOL HEALTH

THE term *school health* is bandied about to such an extent that it never stays still long enough to acquire a definition satisfactory to those involved directly and indirectly in maintaining and administering the health of the school child.

It may be that by escaping a limiting definition, school health has taken into its fold programs not fully within its purview, and bypassed others rightfully belonging in the school-health sphere. The provision of health services for the school child involves so many people and interests that until a common ground of understanding is reached by all concerned, there will inevitably be varying degrees of confusion and conflict. A program involving a school department (from school committee to teacher), parents, family physician and dentist, full or part-time school physician and dentist and local, state and federal governments cannot escape growing pains, both physical and mental and not unsimilar to those that beset the school child.

The Committee on School Health of the Massachusetts Medical Society, recognizing the need for a starting point for the eventual solution of problems involving the administration and provision of health services for school children, is sponsoring, with the co-operation of seven allied organizations, a conference on school health to be held Wednesday, October 17, at the Hotel Statler in Boston.

The program for this initial undertaking in Massachusetts is printed elsewhere in this issue of the *Journal*.

DISTINGUISHED CITIZEN

DR. Charles F. Wilinsky, citizen of the world, seems to have an affinity for honorary degrees, medals and citations, as *Hospitals*, the journal of the American Hospital Association, recently indicated.

In Boston he is known as the former director of the city's famous health units and of the Beth Israel Hospital, which expanded from 178 to 400 beds and became an outstanding teaching and research center under his quarter century of guidance. The country over he is recognized not only for these achievements but as the first man ever to be elected president of both the American Public Health Association and the American Hospital Association, positions that he held consecutively from 1949 to 1951.

And most recently, on September 19, Dr. Wilinsky was awarded by the American Hospital Association its 1956 distinguished service award for meritorious achievement. The medal that goes with this award, although it need not outshine them, will be a fitting companion piece to the Boston City Club's gold medal for "distinguished service to the City of Boston," and the Lemuel Shattuck award of the Massachusetts Public Health Association for distinguished service in the field of public health.

"When love gets into the youthful brain,
Discretion is useless and caution is vain!"
Boston M. & S. J. *October 9, 1856*

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

Active Rheumatic Fever, Pulmonary Infarction and Congestive Heart Failure

A twenty-six-year-old gravida I had a history of rheumatic fever at the age of nineteen. In the thirty-third week of a previously uneventful pregnancy the disease suddenly became decompensated, and she was hospitalized. About twenty-four hours after admission, during which time she improved, labor began, and after two and a half hours, a baby weighing 1.1 kg. (2½ pounds), who survived, was delivered. The post-partum course went smoothly with continuation of oxygen, digitalis, bed rest and sedation. The patient was allowed out of bed on the seventh post-partum day and was discharged with adequate instructions three days later. However, she neglected the recommendations for treatment, perhaps because of a mild mental disturbance. Three days after discharge, again in failure, she was readmitted to the hospital with a temperature of 102°F., a pulse of 150, respirations of 26 and a blood pressure of 160 systolic, 190 diastolic. Treatment with penicillin, oxygen, digitalis, diuretics and chlorpromazine was begun. Each day she improved. She was very well when seen on the tenth morning. However, at about 1 p.m., she had an episode of acute pulmonary edema. Aminophylline and morphine were given; phlebotomy was done and tourniquets were applied to the legs, but she died shortly thereafter.

Autopsy revealed active rheumatic heart disease, rheumatic valvulitis (aortic and mitral) with mitral stenosis, acute pulmonary edema and pulmonary infarction.

This was classified as a preventable death, responsibility being assigned to the patient because she had failed to follow medical advice and, in fact, had been actively refractory to it. The cause of death was active rheumatic fever, superimposed upon existing rheumatic heart disease, decompensated, with pulmonary infarction and the other usual findings of congestive heart failure. The successful management of this case up to the time of delivery, including the excellent immediate post-partum course, deserves congratulations. It becomes evident from the record, however, that excellent advice and careful instructions were ignored when the patient went home. The mild manic-depressive psychosis was hardly a serious contribution to her recalcitrance and may have resulted from relative anoxia. On the other hand, efforts to impress her with the importance of medication and bed rest might have been easier in its absence. Sudden death after apparent improvement is a not uncommon phenomenon in patients whose hearts are severely and actively diseased.

John Figgis Jewett, M.D.
Chairman

NONCLINICAL NOTES

FINLAND AFIELD

In a semiroutine excursion to various of the principal cities of western Europe, editorial colleague Maxwell Finland will visit Milan, Florence, Naples and Rome, where he will lecture on "Antibiotic Therapy" before the medical societies indigenous to those areas; Paris, where he will deliver an address before the Conference on Streptococcus and Rheumatic Fever at the International Children's Center on "Prevention of Rheumatic Fever by Prophylaxis of Streptococcal Infection"; London, where he will lecture on "Some Current Problems in Antibiotic Therapy" before the Harveian Society and on "Antibiotic Resistance" at the Wright-Fleming Institute; and Edinburgh, in which stronghold he will read a paper on "Emergence of Antibiotic-Resistant Bacteria" before the Department of Medicine of the University of Edinburgh.

NOTICES

ANNOUNCEMENT

Dr. Frank Graham Mills announces the opening of his office at 38 Elm Street, Westfield, Massachusetts, for the practice of general surgery.

SOUTH END MEDICAL CLUB

The monthly meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, October 16, at 12 noon.

Dr. David Hurwitz will talk on "Modern Management of Diabetes." All physicians are invited to attend.

AMERICAN PUBLIC HEALTH ASSOCIATION

Progress in preventing health hazards and diseases ranging from highway accidents to the common cold will be reviewed at the annual meeting of the Public Health Association and meetings of 40 related organizations in Convention Hall, Atlantic City, New Jersey, November 12 through 16.

The thirteen sections of the Association have been augmented this year by a new section on mental health. All sections will be responsible for programs in their specialties.

Further information may be obtained from the American Public Health Association, 1790 Broadway, New York, New York.

AMERICAN INSTITUTE OF DENTAL MEDICINE

The annual meeting of the American Institute of Dental Medicine will be held at El Mirador, Palm Springs, California, November 4-8. All seminar lecturers will participate in a round-table forum discussing the application of their subjects to the practice of dental medicine.

Registration should be made as soon as possible.

Further information may be obtained from Miss Marion G. Lewis, Executive Secretary, 2240 Channing Way, Berkeley 4, California.

SOCIETY MEETINGS AND CONFERENCES

OCTOBER 1–31. Consultation Clinics for Crippled Children in Massachusetts. Page 626, issue of September 27.
OCTOBER 4, 5 and 6. Academy of Psychosomatic Medicine. Page 402, issue of August 23.
OCTOBER 5 and 6. New England Surgical Society. Page 489, issue of September 6.
OCTOBER 7, 8 and 9. New Hampshire and Vermont State Medical Societies. Page 304, issue of August 9.
OCTOBER 8–12. American Society of Anesthesiologists. Page 490, issue of September 6.
OCTOBER 8–13. International Cancer Cytology Congress. Page 104, issue of July 12.
OCTOBER 9–13. American Rhinologic Society. Page 490, issue of September 6.
OCTOBER 10. Lahey Clinic Lectures. Page 489, issue of September 6.
OCTOBER 12. New England Rheumatism Society. Page 489, issue of September 6.
OCTOBER 15–17. American College of Gastroenterology. Page 539, issue of September 13.
OCTOBER 15–26. New York Academy of Medicine. Page 304, issue of August 9.
OCTOBER 16. South End Medical Club. Page 675.
OCTOBER 17. Massachusetts Society of Examining Physicians. Page 584, issue of September 20.
OCTOBER 19 and DECEMBER 14, 1956, and FEBRUARY and APRIL, 1957. Massachusetts Society for Research in Psychiatry. Page 56, issue of July 5.
OCTOBER 29. University of Virginia. Page 627, issue of September 27.
OCTOBER 30 and 31 and NOVEMBER 1. New England Postgraduate Assembly, Boston.
NOVEMBER 4–8. American Institute of Dental Medicine. Page 675.
NOVEMBER 12. American Public Health Association. Page 675.
NOVEMBER 12–16. American Public Health Association. Page 402, issue of August 23.
NOVEMBER 14–22. Pan-Pacific Surgical Association. Page 490, issue of September 6.
NOVEMBER 18–22. Pan American Medical Association. Page 490, issue of September 6.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, OCTOBER 11

THURSDAY, OCTOBER 11
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Metabolism Conference. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.
*3:00 p.m. Thoracic Conference. Sensitivity of the Respiratory Center in Chronic Pulmonary Disease. Dr. Eugene D. Robins. Main Amphitheater, Peter Bent Brigham Hospital.
5:00 p.m. Case Presentation and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Auditorium, New England Deaconess Hospital.
5:45 p.m. Medical Journal Club. Joslin Clinic (Cafeteria), New England Deaconess Hospital.

FRIDAY, OCTOBER 12
Holiday

SATURDAY, OCTOBER 13
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*9:00–10:00 a.m. Anesthesiology Conference. Dr. Benjamin Etsten. Anesthesia Laboratory, New England Center Hospital.
*9:30–11:00 a.m. Surgical House Officers' Conference. Second-Floor Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Teaching Ward Rounds. Ward South 2, Free Hospital for Women.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Conference. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, OCTOBER 15
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:00 m. Carney Lecture. Safe and Simple Parenteral Fluid Therapy, Including the Pre- and Postoperative Patient. Dr. Allan M. Butler. Lecture Hall, Carney Hospital, Dorchester.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Metabolism Conference. Dr. Schwartz. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. X-Ray Conference. Dr. William Carey. Saint Elizabeth's Hospital.
*3:00–4:00 p.m. Neuroradiologic Conference. Dr. Bertram Selverstone. Stearns Auditorium, New England Center Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Diagnosis and Treatment of Adrenal Insufficiency. Dr. Thorn's group. Surgical Conference Room, Peter Bent Brigham Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Dr. Benjamin Etsten. Stearns Auditorium, New England Center Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
*7:00–9:00 p.m. Slide Seminar in Pathology. Dr. Edward T. MacMahon. Stearns Auditorium, New England Center Hospital.

TUESDAY, OCTOBER 16
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical Grand Rounds. Pathology Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Medical Grand Rounds. Main Conference Room (Ground Floor), Lemuel Shattuck Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
12:00 m.–1:00 p.m. Staff Conference. Mortality Meeting. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Hematology Conference. Dr. Mario Stefanini. Saint Elizabeth's Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetric). Faulkner Hospital.

WEDNESDAY, OCTOBER 17
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. Deaconess II, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Auditorium, Carney Hospital, Dorchester.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Boston State Hospital Psychiatry Seminar. The Philosophy of Management of Criminals. Mr. Russell G. Oswald. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:00 m.–1:00 p.m. Neurology, Neurosurgery and Psychiatry Conference. Drs. John F. Sullivan, Justin Hope and Bertram Selverstone. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Pediatric Medical-Surgical Rounds. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane, D-Main, Peter Bent Brigham Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overhoit Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*6:00 p.m. Massachusetts Society of Examining Physicians. Harvard Club, Boston.

*Open to the medical profession.